FORMULATION AND EVALUATION OF ORALLY DISINTEGRATING TABLETS OF ONDANSETRON HYDROCHLORIDE

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600032

In partial fulfillment of the requirements for the award of the Degree of

MASTER OF PHARMACY

IN

BRANCH - I - PHARMACEUTICS

Submitted by

R. SUJIN

REG. No. 261510354

Under the guidance of

Dr. M. RAJESH, M.Pharm., Ph.D.,

Professor and Head

Department of Pharmaceutics

SANKARALINGAM BHUVANESWARI COLLEGE OF PHARMACY

ANAIKUTTAM, SIVAKASI – 626130

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OCTOBER 2017

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02.09.2017

TOWHOMSOEVER IT MAY CONCERN

This is to certify that Mr.R.SUJIN Second year M.Pharm student of Sankaralingam Bhuvaneswari College of Pharmacy,Sivakasi has carried out a project on "Formulation and Evaluation of Orally Disintegrating Tablets of Ondansetron Hydrochloride" in our organization between the Period 19.12.2016 to 20.03.2017.

During the period of project He was sincere and dedicative in his project related works. We wish him success in his future career.

For PHARMAFABRIKON Unit II,

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EVALUATION CERTIFICATE

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Internal Examiner **External Examiner**

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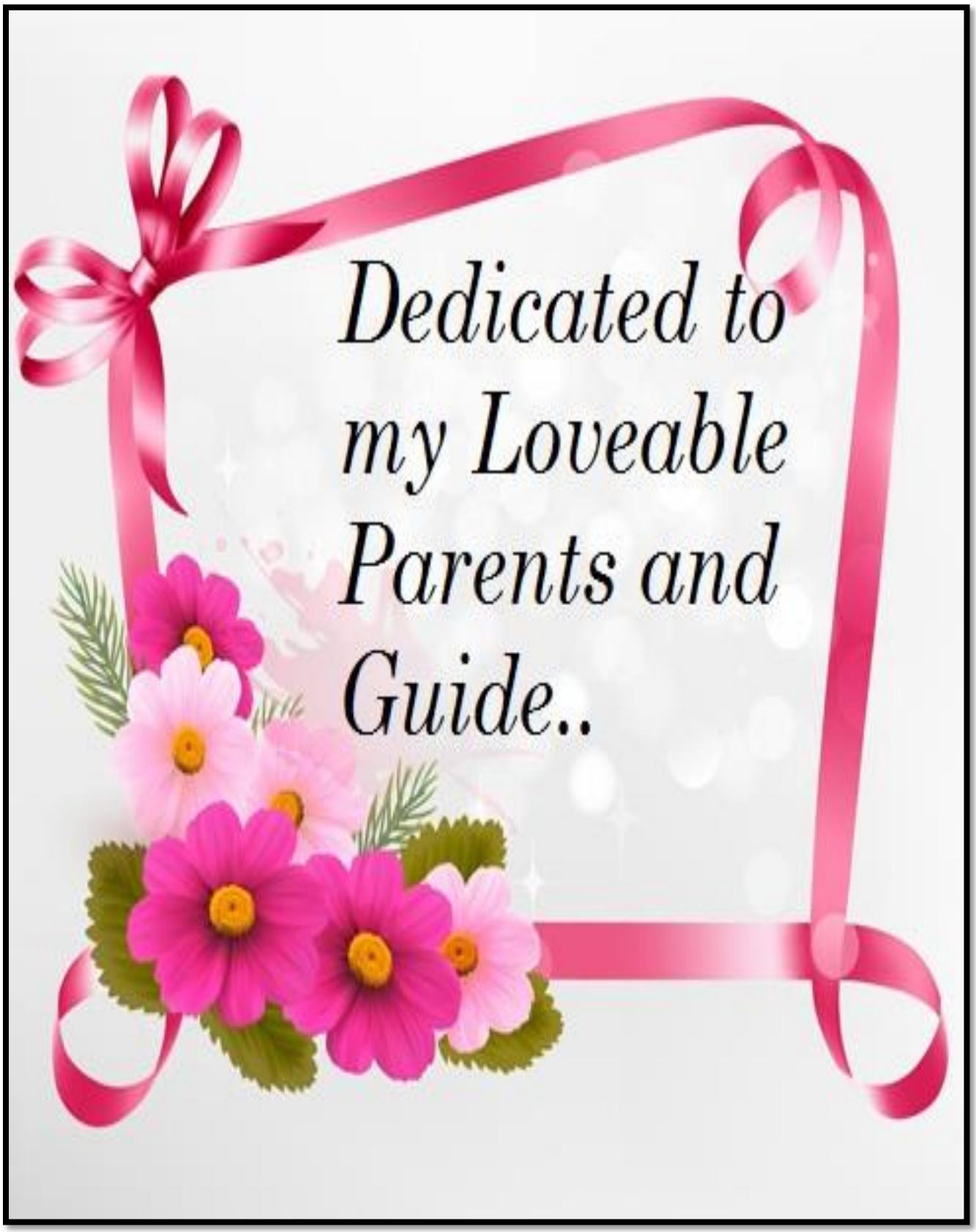
Dedicated to
my Loveable
Parents and
Guide..

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ABBREVIATIONS

ODT^S	Orally Disintegrating Tablets
GIT	Gastro Intestinal Tract
L-HPC	Low Substituted Hydroxy Propyl Cellulose
U.S.P	United State Pharmacopoeia
I.P	Indian Pharmacopoeia
F.D.A	Food & Drug Administration
HPLC	High Performance Liquid Chromatography
UV	Ultra Violet
FT-IR	Fourier Transform Infra-Red Spectrophotometer
API	Active Pharmaceutical Ingredient
ICH	International Council for Harmonization
ACN	Acetonitrile
MCC	Microcrystalline Cellulose
SSG	Sodium Starch Glycolate
CP	Crospovidone
CCS	Croscarmellose Sodium
HCl	Hydrochloric Acid
PVP	Poly Vinyl Pyrrolidone
SCMC	Sodium Carboxy Methyl Cellulose
NLT	Not Less Than
NMT	Not More Than
RT	Retention Time
TD	Tapped Density
BD	Bulk Density
MG	Milligram

RPM	Rotations Per Minute
MM	Milli Metre
µG	Microgram
ML	Milli Litre
NM	Nanometer
GM	Gram
W/V	Weight by Volume

CHAPTER-1

Introduction

CHAPTER-1

INTRODUCTION

1. GENERAL INTRODUCTION[1]

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates) and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. A vast variety of pharmaceutical research is directed at developing new dosage forms for oral administration. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favorite of product development scientists. In similar fashion the oral cavity is highly acceptable by patients, the mucosa is relatively permeable with rich blood supply and virtual lack of langerhans cells makes oral mucosa tolerant to potential allergens.

1.1. SOLID DOSAGE FORMS

Drugs are rarely administered solely as pure chemical substances, but are almost given as formulated preparations. The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in the formulation.

Before a drug substance can be successfully formulated into a dosage form, many factors must be considered. These factors can be broadly grouped into 3 categories[2],

1. Biopharmaceutical considerations (Factors affecting absorption of drugs)
2. Drug related factors (Physical and Chemical properties of the drug)
3. Therapeutic considerations (Disease to be treated and Patient factors)

Among various orally administered dosage forms (tablets, capsules, syrup, solution etc…) the tablet dosage form is the most widely used.

Solid dosage form is one type of physical dosage forms mainly administrated orally in dry state. Some of the solid dosage forms are shown below [3].

- Tablets
- Capsules
- Pills
- Pastilles
- Lozenges
- Cachets or powder

As these contain a quantity of drug which is given as a single unit they are known collectively as solid unit – dosage forms[4].

1.1.1. TABLETS

A tablet is a compressed solid unit dosage form containing medicaments with or without excipients. According to the Indian pharmacopoeia, pharmaceutical tablets are solid flat or biconvex dishes prepared by compressing a drug or a mixture of drugs, with or without diluents[5].

They vary in shape and differ greatly in size and weight, depending on the amount of medical substance and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablets. Tablets offer advantages over both patients and manufacturers. Tablets are the most popular dosage form due to their simplicity and economy of manufacture, relative stability and convenience in packaging, shipping and storage. Ease of manufacturing, convenience in administration, accurate dosing and stability compared to oral liquids, tamper proofness compared to capsules and safety compared to parentral dosage forms makes it a popular and versatile dosage form[6].

1.1.1.1. ADVANTAGES OF TABLETS[7]

The primary potential advantages of tablets are

- They are the unit dosage forms, which offer the great capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- The cost is lowest of all oral dosage forms.
- They are the lightest and most compact of all.
- They are in general the easiest and cheapest to packaging and shipment.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They may provide the greatest ease of swallowing with the least tendency for hang up above the stomach, especially when coated, provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products, such as enteric or delayed release products.
- They are better suited to large scale production than with other unit oral dosage forms.
- They have the best combined properties of chemical, mechanical and microbiological stability of all the oral forms.

1.1.1.2. DISADVANTAGES OF TABLETS

Inspite of all these advantages, tablets also possess some disadvantages. This includes the following

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent and low density character.
- Drugs with poor wetting properties, slow dissolution properties, intermediate to large dosages, poor absorption in the GIT or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet.
- Bitter tasting drugs, drug with obnoxious odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation / entrapment prior to compression / coating.

1.1.1.3. CLASSIFICATION OF TABLETS

a) Classification based on mode of administration

1) Tablets to be swallowed
2) Chewable tablets
3) Tablets used in oral cavity
    a) Buccal tablets
    b) Sublingual tablets
    c) Troches and lozenges
    d) Dental cones
4) Tablets administered other than oral route
    a) Implants
    b) Vaginal tablets / suppositories

b) Classification based on drug manufacturing process

1) Standard compressed tablets
2) Multiple compressed tablets
    a. Compression – coated tablets
    b. Layered tablets
3) Coated tablets
4) Molded tablets (Tablet triturates)

c) Classification based on drug release profile

1) Fast Dissolving tablets
2) Immediate Release tablets
3) Controlled/ Sustained Release tablets
4) Delayed Release tablets (Enteric coated tablets)

d) Tablets used to prepare solutions

a) Effervescent tablets
b) Dispersible tablets

1.1.1.4. TABLET EXCIPIENTS[8]

The excipients are classified according to the function. They include the following.

a) Fillers / Diluents
b) Binders
c) Disintegrants
d) Lubricants
e) Glidants
f) Anti-adherents / anti-adhesives
g) Colouring agents

The details of the tablet excipients are shown in table: 1

Table: 1 Tablet Excipients

Excipient category	Applications	Working principle	Examples
Diluents	Fillers	Make up the bulk of solid unit dosage forms when drug itself is inadequate to produce the bulk	Lactose, Directly compressible Starches, Dextrose, Sorbitol, Microcrystalline cellulose, Dibasic Calcium phosphate (dehydrate).
Binders and Adhesives	Impart cohesive qualities to powdered material.	Improves free flow qualities by formulation of granules to desired hardness and size.	Acacia, Gelatin, Starch paste, Polyvinyl pyrrolidone, Glucose, Carboxymethyl cellulose.
Lubricants	Reduce inter-particular friction, prevent adhesion of tablet material to the surface of dies and punches, facilitate easy ejection of tablet from die cavity and improve the rate of flow of granules.	Interpose a film of low shear strength between the tabletting mass and die wall	Talc, Stearic acid, Magnesium stearate, Calcium stearate, Polyethylene glycol, Surfactants, vegetable oil.
Glidants	Improve flow characteristics of powder mixture.	Added in dry state prior compression, it reduces friction between particles	Colloidal Silicone dioxide (Carbosil), Asbestos free starch, Corn starch.
Disintegrants Superdisintegrants	Facilitate breakup or disintegration after administration. Improve disintegrant efficacy resulting in decreased use levels when compared to traditional disintegrants.	Function by drawing water into the tablet, swelling it and causing the tablet to burst apart	Starches, Clays, Cellulose, Cross linked polymers, Modified starches such as Primogel and Explotab, Veegum HV, Crosscarmalose, Cross Povidone, Sodium starch glycolate.
Coloring agents (these must be approved and certified by FDA)	Impart aesthetic appearance to dosage form, disguising off color drugs, product identification.	Color is a useful tool to help and identify a product in its manufacturing and distribution stages.	FD and C, D and C dyes and lakes.

1.1.1.5. TABLET MANUFACTURING PROCESS[9]

An outline of the various steps involved in the manufacturing of tablets by different methods is mentioned below in Table: 2

Table: 2 Tablet Manufacturing Process

Wet Granulation	Dry Granulation	Direct Compression
Milling of drugs and excipients	Milling of drugs and excipients	Milling of drugs and excipients
Mixing of milled products	Mixing of milled products	Mixing of milled products
Preparation of the binder solution	Compression into large hard tablets called slugs	Tablet compression
Mixing binder solution with powder mixture to form wet mass	Screening of slugs	-
Coarse screening of wet mass	Mixing with lubricant and disintegrating agent	-
Drying moist granules	Tablet compression	-
Screening dry granules with lubricant and disintegrant	-	-
Mixing Screened granules with lubricant and disintegrant	-	-
Tablet compression	-	-

The various process involved in the manufacturing of tablet are,

- Mixing
- Granulation
- Drying
- Milling
- Compression

Mixing[7]

Almost every pharmaceutical product contains more than one component and this necessitates mixing or blending stages in their manufacturing process.

Mixing is defined as a process "in which two or more ingredients in separate or roughly mixed condition are treated so that each particle of any one ingredients in as nearly as possible adjacent to a particle of each of the other ingredients."

Types of mixers

a) Batch type

Twin-shell, Double cone, Ribbon, Planetary, Fluidized air.

b) Continuous

Zigzag, Barrel, Blendex.

Granulation[10]

Granulation is a process making separate powder particle into a group by using granulating fluid. Granulating fluid may be water including or water heating, this depends on the nature of drug and other excipients used. The process of making of granules is termed as granulation and the technique and equipment used is granulation technology.

Reasons for Granulation[11]

- To improve powder flow.
- To improve compressibility.
- To reduce fines.
- To control the tendency of powders to segregate.
- To control density.
- To capture and fuse small quantities of active material

Types of Granulation[12]

- Wet Granulation.
- Dry Granulation.
- Direct Compression.

Wet Granulation

This is the most widely used method of tablet preparation. In this method the powders are bound by suitable binder by "adhesion". The binder is added by diluting with suitable solvent prior to addition to the blended powders to form wet granules which in turn are dried suitably to expel the solvent to form dried granules. The surface tension forces and capillary pressure are primarily responsible for initial granules formation. The main advantage being it meets all the requirements for tablet formation though it is multistage, time consuming process.

Dry Granulation

The dry granulation process is used to form granules without using a liquid solution. This type of process is recommended for products, which are sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be done on a tablet press using slugging tooling.

Direct Compression

The tablets are made by directly compressing the powdered materials without modifying the physical nature of the materials itself. Direct compression is generally done for the crystalline materials having good physical properties such as flow property, compressibility etc. Main advantages of direct compression are time saving, safety of operations and low cost.

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Compression[7]

The ultimate test of a tablet formulation and granulation process is whether the granulation can be compressed on a high- speed tablet press.

During compression, the tablet press performs the following functions:

- Filling of die cavity.
- Precompression of granulation.
- Compression of granulation.
- Ejection of the tablet from the die cavity and take-off of compressed tablet.

1.1.1.6. PROBLEMS IN TABLETING[14]

- Capping and Lamination
- Picking and Sticking
- Mottling
- Double impression

Capping and Lamination

Capping is a term used to describe the partial or complete separation of the top or bottom crowns of a tablet from the main body of the tablet. Lamination is the separation of a tablet into two or more distinct layers.

Picking and Sticking

Picking is a term used to describe the surface material from a tablet that is sticking to and being removed from the tablet's surface by a punch. Sticking is the adhesion of granulation material to the die wall.

Mottling

Mottling is an unequal distribution of colour on a tablet, with light or dark areas standing out in another wise uniform surface.

Double Impression

This involves only punches that have monogram or other engraving on them. At the moment of compression the tablet receives the imprint of the punch. Sometimes it will receive double impression due to improper movement of lower punch.

Preventive Methods:

- By proper mixing
- By improving the flow properties of granules
- By using proper camtracks which are responsible for punches movements.

1.1.1.7. EVALUATION OF TABLETS

Tablets formulated may undergo physical and chemical changes thereby altering the bioavailability of the dosage form. These tablets are to be evaluated before dispensing to maintain their stability and bioavailability throughout its shelf life. Evaluation of tablets can be carried as follows:

a) Unofficial tests

- Tablet appearance
- Organoleptic properties
- Identification markings on tablet
- Size and shape of the tablet
- Thickness of tablet
- Hardness of tablet
- Friability of tablet

b) Official tests

- Weight variation test
- Content uniformity test
- Disintegration test
- Dissolution test

1.2 ORALLY DISINTEGRATING TABLETS

1.2.1. DEFINITION [15, 16]

Orally Disintegrating Tablets (ODT^S) tablets are defined as uncoated or film coated tablets intended to be dispersed in water before administration giving a homogenous dispersion. Typically a tablet is dispersed in about 5-15 ml of water and the resulting dispersion is administered to the patients. Dispersible tablets are required to disintegrate within 3 minutes in water at 15-25^oC.

1.2.2. BACKGROUND OF THE INVENTION[16]

Tablets and capsules are convenient pharmaceutical dosage forms for manufacturing, storage and ensure dosage uniformity. However, such dosage forms, like capsule and tablets, often present ingestion problems such as difficulty in swallowing, particularly for paediatric and geriatric populations. This may result in a high incidence of non- compliance and ineffective therapy, which may prove to be fatal in case of serious conditions. Suspension dosage forms could solve this problem, but they have other associated drawbacks like lower physical and chemical stability and high cost of manufacturing. Suspensions are also inconvenient to carry while travelling and also involve the risk of inaccurate measurement and dosing. Thus, there is need for oral pharmaceutical composition, which can be taken orally without need of swallowing it and act as a viable substitute for suspensions. Accordingly, provided are water dispersible tablet compositions, which can either be chewed or can be readily dispersed before oral administration. One of the key requirements of water dispersible tablet is that they should dissolve in an aqueous medium within a short time period of, for example, less than three minute, to form a smooth suspension without any coarse lumps. Dispersible tablets provide advantages of both tablets and liquid formulations. These are convenient to carry, easy to manufacture and more stable.

1.2.3. ODT^{S} TERMINOLOGY[17]

Orally disintegrating tablets are also known as mouth dissolving tablets, orodispersible tablets, fast disintegrating tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, quick melt tablets or rapid melt tablets.

1.2.4. ADVANTAGES OF ODT^{S} [18]

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric, mentally ill, disabled and uncooperative patients.
- Rapid dissolution of drug and absorption may produce rapid onset of action. Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance by reducing side effects.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
- Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach; in such cases bioavailability of these drugs increases.
- Good mouth feel property of ODT^{S} helps to change the psychology of medication as “bitter pill” particularly in pediatric patients.
- Ability to provide advantages of liquid medication in the form of solid preparation.

1.2.5. DISADVANTAGES OF ODT^{S}

- Rapid disintegrating tablets are hygroscopic in nature so must be kept at controlled environment i.e. humidity and temperature.
- For proper stability and safety, ODT^{S} requires special packaging.
- They usually have insufficient mechanical strength. Hence, careful handling is required.
- Leave unpleasant taste and/or grittiness in mouth if not formulated properly.

1.2.6. CHALLENGES IN FORMULATING ODT^S

Palatability[19]

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

Mechanical strength[20]

In order to allow ODT^S to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.

Hygroscopicity

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Amount of drug

The application of technologies used for ODT^S is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Aqueous solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablet[21]

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Mouth feel[22]

The particles produced after disintegration of the ODT^S should be very small. ODT^S should not leave any residue in the mouth after oral administration. Addition of flavors and cooling agents like menthol enhance the mouth feel.

Sensitivity to environmental conditions:

ODT^S should have low sensitivity to environmental conditions such as humidity and temperature.

Cost factor

The technology adopted for an ODT^S should be acceptable in terms of cost of the final product.

1.2.7. PATIENT FACTORS[23]

Orally disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with water. These include the following:

- Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an a typical antipsychotic.
- A patient with persistent nausea, who may be in a journey or has little or no access to water.

1.2.8. EFFECTIVENESS FACTOR[24, 25]

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pregastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs[21.] Any pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and pregastric segments of GIT[22].

1.2.9. MANUFACTURING AND MARKETING FACTORS[26]

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size. As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and under-treated patient populations.

Marketers build a better brand and company image when they offer a unique easier-to-take form that satisfies the need of an underserved patient population.

1.2.10. IDEAL PROPERTIES[27]

An orally disintegrating tablet should

- Require no water for oral administration, yet dissolve/disperse/disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be harder and less friable.
- Leave minimal or no residue in mouth after administration. Exhibit low sensitivity to environmental conditions (temperature and humidity).

- Allow the manufacture of tablet using conventional processing and packaging equipment's. Benefits of ODT[S] was given below fig: 1

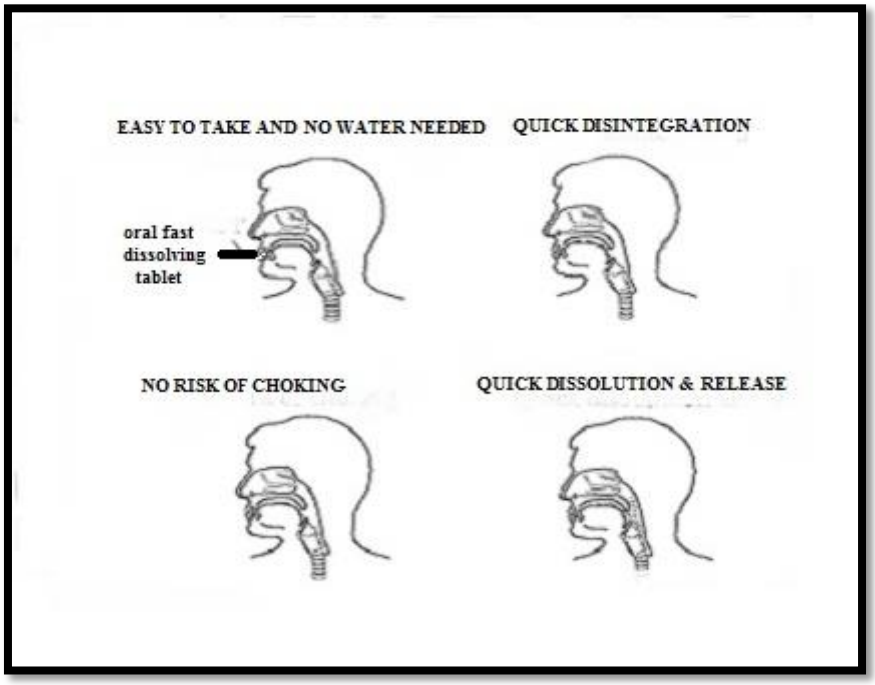

Fig: 1 Benefits of Orally Disintegrating Tablets

1.2.11. DISINTEGRANTS IN DISPERSIBLE TABLETS[28]

Disintegrants are agents added to tablet formulations to promote the break-up of the tablet into smaller fragments in an aqueous environment, thereby increasing the available surface area and promoting a more rapid release of the drug substance. In more recent years, several newer disintegrants have been developed, often called "super disintegrants". These newer substance can be used at lower levels than conventionally used disintegrants. Three major mechanisms and factors affecting tablets disintegrants are suggested as swelling, porosity and capillary action and deformation. Three major group of compound that have been developed as superdisintegrants are modified starches, cross-linked polyvinylpyrrolidone and modified cellulose.

1.2.12. SUPERDISINTEGRANTS[29]

In dispersible tablets, disintegrants plays a major role. Disintegrating agents are substances routinely included in the tablet formulations to aid in the breakup of the compacted mass when it is put into a fluid environment. They promote moisture penetration and dispersion of the tablet matrix. In recent years, several newer agents have been developed known as "Superdisintegrants". These newer substance are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose.

1.2.12.1. SELECTION OF SUPERDISINTEGRANTS

Although superdisintegrants increase the rate of disintegration, but when used at high levels they can affect mouth feel, tablets hardness and friability. Hence, various ideal factors are to be considered while selecting an appropriate superdisintegrants for a particular formulation. A superdisintegrant should,

- Produce rapid disintegration, when tablet comes in contact with saliva in the mouth/oral cavity.
- Be compatible enough to produce less friable tablets.
- Produce good mouth feel to the patients. Thus, small particle size is preferred to achieve patient compliance.
- Have good flow, since it improves the flow characteristics of total blend.

1.2.12.2. SUPERDISINTEGRANTS USED IN TABLETS[30]

Modified Starches

Sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch. It is effective at a concentration of 2-8%. It can take up more than 20 times its weight of water and the resulting high swelling capacity combined with rapid uptake of water accounts for its high disintegration rate and efficiency. It is available in various grades as Type A, B and C which differ in pH, viscosity and sodium content. Other special grades are available which are prepared with different solvents and thus the product

has a low moisture (<2%) and solvent content (<1%), thereby being useful for improving the stability of certain drugs.

Modified Celluloses, Carboxymethylcellulose and its derivative

Cross-linked sodium carboxymethylcellulose is a white, free flowing powder with high absorption capacity. It has a high swelling capacity and thus provides rapid disintegration and drug dissolution at lower levels. It also has an outstanding water wicking capacity and its cross-linked chemical structure creates an insoluble hydrophilic, highly absorbent material resulting in excellent swelling properties. Its recommended concentration is 0.5-2.0%, which can be used up to 5.0%. L-HPC (Low substituted hydoxy propyl cellulose) is insoluble in water, swells rapidly and is used in the range of 1-5%. The grades LH- 11 and LH- 21 exhibit the greatest degree of swelling.

Cross-linked Polyvinylpyrrolidone

It is a completely water insoluble polymer. It rapidly disperses and swells in water but does not gel even after prolonged exposure. The rate of swelling is highest among all the superdisintegrants and is effective at 1-3%. It acts by wicking, swelling and possibly some deformation recovery. The polymer has a small particle size distribution that imparts a smooth mouth feel and dissolves quickly. Varieties of grades are available commercially as per their particle size in order to achieve a uniform dispersion with the formulation.

Soy Polysaccharide

It is a natural superdisintegrant that does not contain any starch or sugar, so can be used in nutritional products.

Cross-linked Alginic acid

It is insoluble in water and disintegrates by swelling or wicking action. It is a hydrophilic colloidal substance, which has high sorption capacity. It is also available as salts of sodium and potassium**.**

Gellan gum

It is an anionic polysaccharide of linear tetrasaccharides, derived from Pseudomonas elodea having good superdisintegrant property similar to the modified starch and celluloses.

Xanthan gum

Xanthan Gum derived from Xanthomonas campestris is official in USP with high hydrophilicity and low gelling tendency. It has low water solubility and extensive swelling properties for faster disintegration.

Calcium silicate

It is a highly porous, light weight superdisintegrant, which acts by wicking action**.**

Ion exchange Resins

The INDION 414 has been used as a superdisintegrant for ODT^{S}. It is chemically cross-linked polyacrylic, with a functional group of COO^{-} and the standard ionic form is K^{+}. It has a high water uptake capacity.

Other Superdisintegrants

Although there are many superdisintegrants, which show superior disintegration, the search for newer disintegrants is ongoing and researchers are experimenting with modified natural products like Formalin, Casein, Chitosan, Polymerized agar acryl amide, Xylan, Smecta, Key-jo-clay, Crosslinked carboxymethylguar and modified Topioca starch.

The different superdisintegrants used for the preparation of ODT^{S} are presented in Table 3.

Table 3: Superdisintegrants used in the Preparation of ODT^{S} [31]

Name	Composition	Mechanism of action	Special comment
Croscarmellose (Ac-Di-Sol, Nymce ZSX, Primellose®, Solutab)	Cross linked Cellulose	Swells 4-8 folds in < 10 seconds. Both swelling and wicking.	Swells in two dimensions.
Crospovidone (Crospovidone M, Kollidon, Polyplasdone)	Cross linked PVP	Swells very little and returns to original size after compression but act by capillary action.	Water insoluble and spongy in nature, produce porous tablet.
Sodium starch glycolate (Explotab, Primogel)	Cross linked Starch	Swells 7-12 folds in < 30 seconds.	Swells in three dimensions and high level serve as sustain release matrix.
Alginic acid NF (Satialgine)	Cross linked alginic acid	Rapid swelling in Aqueous medium, wicking action.	Promote disintegration in both dry or wet Granulation.
Soy polysaccharides (Emcosoy)	Natural superdisintegrant	Swelling action	Does not contain any starch or sugar. Used in nutritional products.
Calcium silicate	Silicate	Wicking action	Highly porous, Optimum concentration is between 20-40%.

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1.2.12.3. MECHANISM OF SUPERDISINTEGRANTS [32, 33]

There are 4 major mechanisms for tablets disintegration and they are as follows:

1. Swelling
2. Porosity and Capillary action (Wicking)
3. Disintegrating particle/particle repulsive forces
4. Deformation

SWELLING

The general mechanism of action for tablet disintegration, which is most widely accepted, is swelling. Tablets with high porosity due to lack of adequate swelling force show poor disintegration. Sufficient swelling force with low porosity is exerted in the tablet with low porosity.

WICKING

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the preparation of fluid into tablets. The disintegrant particles themselves act to enhance porosity and provide pathways into the tablet. Liquid is drawn up or "wicked" into these pathways through capillary action and rupture the interparticulate bonds causing the tablet to break apart.

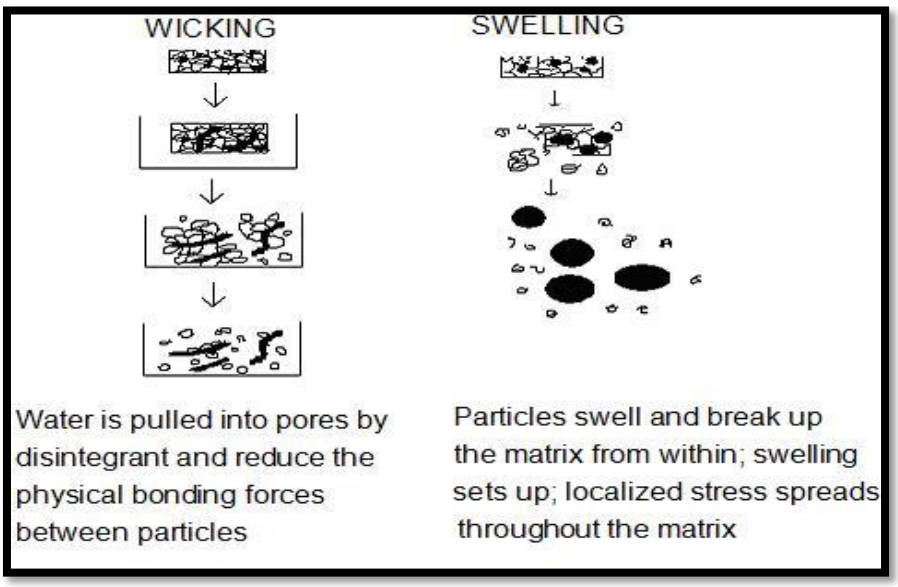


Fig: 2. Disintegration of Tablets by Wicking and Swelling Mechanism

PARTICLE- PARTICLE REPULSIVE FORCES

Another mechanism of disintegrant attempts to explain the swelling of tablet made with 'nonswellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

DEFORMATION

Disintegrated particles get deformed; during compression of tablets and when these deformed particles come in contact with aqueous media or water they get into their normal structure. Swelling capacity of starch was improved during compression. The increase in size of the deformed particles produces breakup of tablets.

The Mechanism of Deformation and Repulsion during the disintegration of tablets are shown in Fig: 3

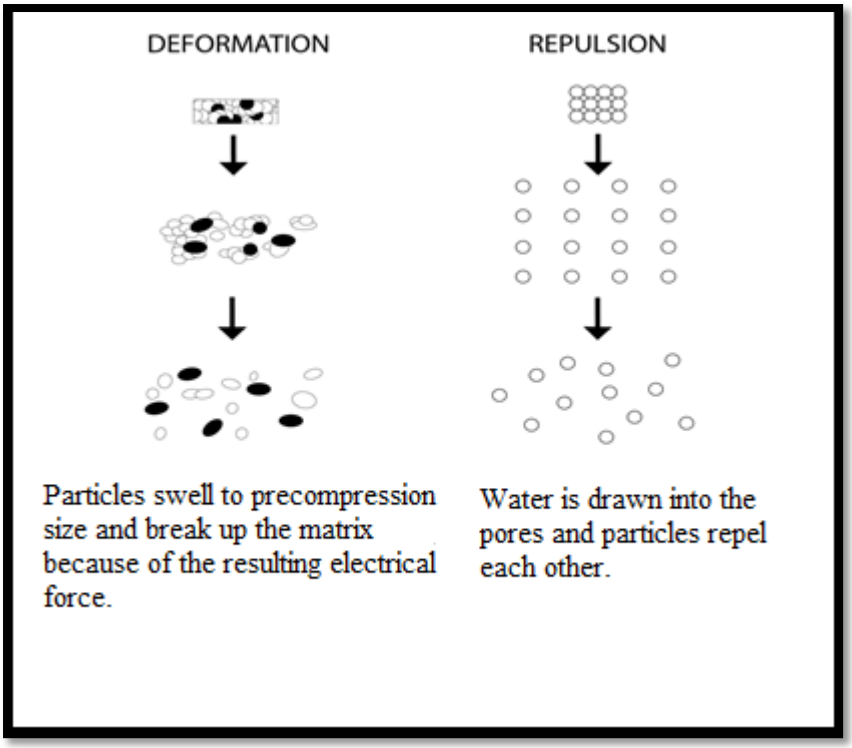


Fig: 3. Disintegration of Tablet by Deformation and Repulsion Mechanism

1.2.13. TECHNIQUES FOR FORMULATION OF ORALLY DISINTEGRATING TABLETS [34]

Many techniques have been reported for the formulation of orally disintegrating tablets.

1. Freeze drying / Lyophilization
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion

FREEZE DRYING

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT^S using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is poured in the walls of the performed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally the blisters are packed and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

TABLET MOULDING

Molding process is of two types (solvent method and heat method). Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and possess a porous structure that hastens dissolution. The heat molding process involves

preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded tablets is a matter of great concern. Binders, which increase the mechanical strength of the tablets, needs to be incorporated. Taste masking is an added problem to this technology. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the molding technique are easier to scale up for industrial manufacture.

SPRAY DRYING[35]

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose or crospovidone are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation may contain bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate (or) croscarmellose sodium, acidic ingredient (citric acid) and alkaline ingredient (e.g. sodiumbicarbonate). This spray-dried powder, when compressed into tablets may produce rapid disintegration and dissolution.

SUBLIMATION

In this method to generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec.

DIRECT COMPRESSION[36]

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can be applied to preparation of ODT[S] because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

(a)Super Disintegrants:

In many orally disintegrating tablets technologies based on direct compression, the addition of superdisintegrants increase the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further hastens the process of disintegration.

(b)Sugar Based Excipients:

This is another approach to manufacture ODT[S] by direct compression method. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol will display high aqueous solubility and sweetness and hence impart taste masking property and a pleasing mouth feel. Mizumito *et al* have classified sugar-based excipients into 2 types on the basis of molding and dissolution rate.

Type 1 Saccharides (lactose and mannitol) exhibit low mould ability but high dissolution rate.

Type 2 Saccharides (maltose and maltilol) exhibit high mould ability and low dissolution rate.

MASS EXTRUSION[37]

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments and using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

1.2.14. PATENT TECHNOLOGIES FOR ORALLY DISINTEGRATING TABLETS[38]

1. Zydis Technology
2. Durasolv Technology
3. Orasolv Technology
4. Wow tab Technology
5. Flash Dose Technology
6. FlashTab Technology
7. Oraquick Technology
8. Nanocrystal Technology

Zydis Technology

It was patented by Zydis. In this technology, the drug is entrapped within the matrix of fast dissolving carrier. The product is a unique freeze dried tablet that dissolves on tongue within 2-3 sec.

Durasolv Technology

It was patented by CIMA Labs. In this technology, drug is mixed with fillers and lubricant and tablets ware prepared using conventional tableting machines.

Orasolv Technology

It was also patented by CIMA Labs. This technology produces tablets comprising of taste masked medicaments and effervescent disintegrating agents prepared by direct compression method.

Wow Tab Technology[39]

It was patented by Yamanouchi Pharmaceutical Co. WOW refers to With out Water. This technology utilizes combinations of low and high mouldability saccharides to obtain rapidly melting tablets.

Flash Dose Technology

It was patented by Fuisz. This technology produces tablets consisting of self-binding shear form matrix called as “floss” prepared by flash heating process.

FlashTab Technology

It was patented by Prographarm laboratories. In this technology, active ingredients are made into microgranules using techniques like coacervation or microencapsulation and tableted using conventional technology.

Oraquick Technology

It was patented by KV Pharmaceuticals. In this technology, drug is microencapsulated and surrounded by a matrix making it more pliable.

Nanocrystal Technology

Rate of dissolution can be increased by decreasing the particle size. In this technology, drugs are milled to small particles <1000 nm which is then combined with water soluble ingredients, lyophilized and finally blister packed.

1.2.15. STAGES OF DISINTEGRATION

The different stages of disintegration of ODT^{S} were shown in Fig: 4

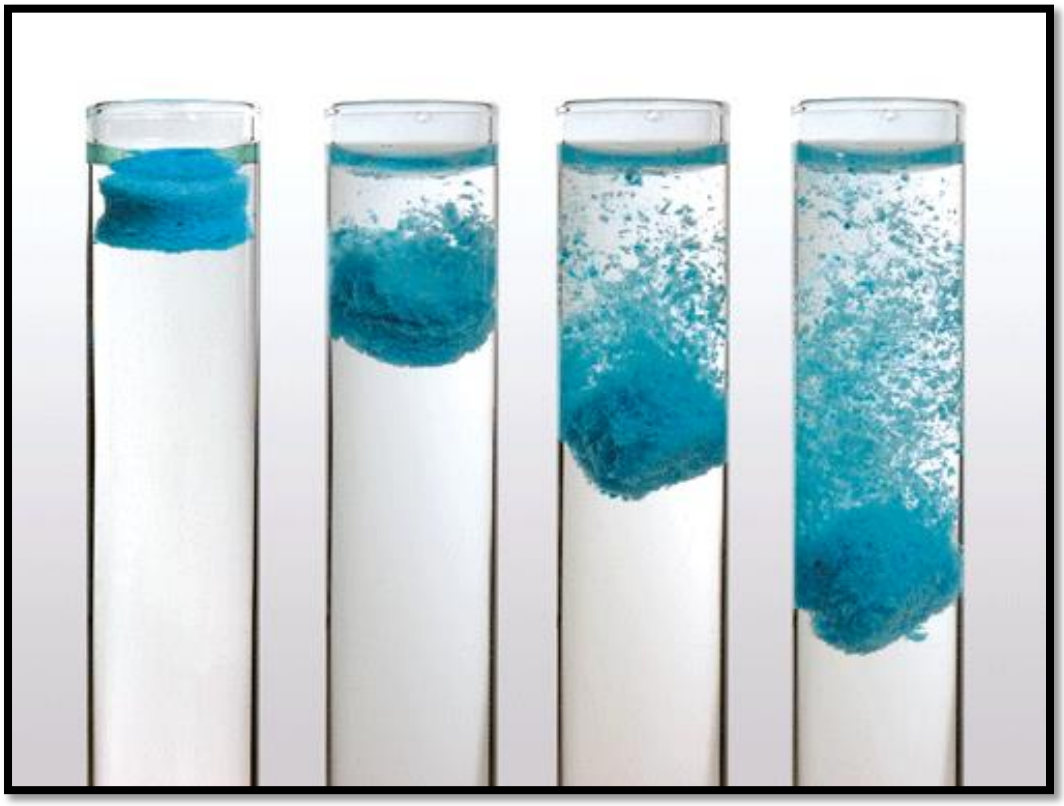


Fig: 4 Disintegration Stages of Dispersible Tablets

1.2.16. EVALUATION OF ORALLY DISINTEGRATING TABLETS [40]

Hardness

A significant strength of ODT^S is difficult to achieve due to the specialized processes and ingredients used in the manufacturing. The limit of hardness for the ODT^S is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness test.

Friability

To achieve % friability within the limit for an ODT^S is a challenge for a formulator since all the methods of manufacturing ODT^S are responsible for increase in the % friability values. Thus, it is necessary that this parameter should be evaluated and the results should be within bound limits (0.1-0.9%).

Wetting time and Water absorption ratio

Wetting time of dosage form is related with the contact angle. Wetting time of the ODT^S is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure. Five circular tissue papers of 10cm diameter are placed in a petri dish. Ten milliliters of water soluble dye solution is added to petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ratio the weight of the tablet before keeping in the petri dish is noted (Wb). The wetted tablet from the petri dish is taken and reweighed (Wa). The water absorption ratio, *R* can be the determined according to the following equation.

$$R = 100 \text{ (Wa-Wb) / Wb}$$

Moisture uptake studies

Moisture uptake studies for ODT^S should be conducted to assess the stability of the formulation. Ten tablets from each formulation were kept in a desiccator over calcium chloride at 37^0 C for 24h. The tablets were then weighed and exposed to 75% relative humidity, at room temperature for 2 weeks. Required humidity was achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for 3 days. One tablet as control (without superdisintegrant) was kept to assess the moisture uptake due to other excipients. Tablets were weighed and the percentage increase in weight was recorded.

Disintegration test

The time for disintegration of ODT^S is generally<1min and the actual disintegration time that patients can experience ranges from 5 to 30s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT^S should mimic disintegration in mouth with in salivary contents.

Dissolution test

Dissolution media such as 0.1 N HCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT^S in the same way as their ordinary tablet counter parts. USP dissolution apparatus 2 (paddle) is most suitable and common choice for dissolution test of ODT^S tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODT^S is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. The USP dissolution apparatus 1 (basket) may have certain applications for ODT^S but is used less frequently due to specific physical properties of tablets. Specifically tablet fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile.

CHAPTER-2

Review of Literature

CHAPTER - 2

REVIEW OF LITERATURE

Avani R. Gosai *et al.*, (2008)[41] formulated and evaluated oro dispersible tablets of Ondansteron hydrochloride by direct compression method. The tablets were prepared by using sodium starch glycolate and croscarmellose sodium as superdisintegrants. Microcrystalline cellulose was used as diluent. Mannitol, mint flavor, sodium saccharin were used to enhance the organoleptic properties of tablets. The tablets were evaluated for post compression parameters such as weight variation, friability hardness, *in vitro* disintegration time, *in vivo* disintegration time, wetting time and drug release characteristics. All the parameters were found within the U.S.P limits. Hardness and friability data indicated good mechanical strength of tablets. The results showed *in vitro* disintegration time and *in vivo* disintegration time of the tablets was within 3 to 5 seconds. Dissolution study revealed faster drug release rate of Ondansetron hydrochloride from the tablets as compared with marketed conventional tablet of Ondansetron hydrochloride. The study concluded that batch S_2C_2 showed 98.63% drug release at the end of 30 minutes and emerged as best formulation.

Mohammad Ali Shahtalebi *et al.*, (2015)[42] formulated and evaluated an orally disintegrating tablet containing Ondansetron by using semisynthetic and natural superdisintegrants. Orodispersible tablets were prepared by direct compression using natural superdisintegrant (Karaya gum) and semi-synthetic superdisintegrant (croscarmellose). The prepared tablets were evaluated for hardness, friability, thickness, drug content uniformity, wetting time and water absorption ratio. According to the results of optimized batches, the best concentrations of superdisintegrants (7.88 mg karaya gum and 7.78 mg croscarmellose) gave rapid disintegration in 31 seconds and showed 99% drug release within 5 minutes. The study concludes that karaya gum, a natural superdisintegrant, gives rapid disintegration and high release when used with synthetic superdisintegrant in the formulation of ODT^S.

Sheshala R *et al.*, (2011)[43] formulated taste-masked orally disintegrating tablets of Ondansetron, a bitter drug using different superdisintegrants by wet granulation technique. Microcrystalline cellulose (Avicel) as diluent and disintegrant in addition to aspartame as a sweetener were used in all formulations. The prepared tablets were evaluated for weight variation, thickness, hardness, friability, drug content, water content, *in vitro* disintegration time and *in vitro* drug release. The tablets hardness were maintained in the range of 2-3 kg and friability was <1% for all batches. All formulations disintegrated rapidly *in vitro* within 5.83 to 33.0 seconds. The optimized formulation containing 15% Polyplasdone XL-10 released more than 90% of drug within 5 minutes and the release was comparable to that of a commercial product. In human volunteers, optimized formulation was found to have a pleasant taste and mouth feel and they disintegrated in the oral cavity within 12 seconds. The stability results were also found to be satisfactory. A pharmacokinetic study with the optimized formulation was performed in comparison with a reference (Zofer MD 8®) and they were found to be bioequivalent. In conclusion, a cost effective Ondansetron orally disintegrating tablet was successfully prepared with acceptable hardness, desirable taste and rapid disintegration in the oral cavity.

Nitin Bansal *et al.*, (2011)[44] developed orally disintegrating tablets of Ondansetron HCl by dry granulation method using different concentrations of superdisintegrants such as modified gum karaya, modified natural agar, croscarmellose sodium and sodium starch glycollate. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, *in vitro* disintegration time and *in vitro* dissolution study. The results showed that modified gum karaya and modified natural agar produce rapid disintegration of tablets. The optimized formulation showed acceptable physical characteristics and produced complete drug release within 6 minutes. The incorporation of clove oil provided additional properties such as symptomatic relief from nausea and vomiting, good mouth feel and taste masking. Kinetic analysis showed that drug release from optimized formulation was adequately described by first order release kinetics. The results revealed that modified gum karaya and modified natural agar can be used as an alternative superdisintegrants to commonly available synthetic and semisynthetic superdisintegrants due to their low cost, biocompatibility as well as easily availability.

Suresh *et al.*, (2007)[45] prepared and evaluated Salbutamol sulphate ODT^S for asthma by wet granulation method using sublimable components *viz* camphor and ammonium bicarbonate. The prepared tablets were evaluated for weight variation, hardness, friability, drug content and disintegration time. All the prepared tablets disintegrated in less than a minute. The formulations tested for all the evaluation parameters were found to be within the I.P limits. Formulation F3 showed minimum disintegration time of 5 seconds and emerged as best formulation.

Kitawat S *et al.*, (2013)[46] reviewed an increasing demand for more patient compliant dosage form and a novel method is the development of orally disintegrating tablets which dissolve or disintegrates instantly on the patient tongue or buccal mucosa. It is suited for tablets undergoing high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to minimize side effect and make it more cost effective. Oral route having the highest patient compliance is regarded as the most convenient, safest and also the most economical method of drug delivery.

Radke R.S *et al.*, (2009)[47] prepared orodispersible tablets of Baclofen using various concentrations of superdisintegrants like Ac-Di-Sol, crospovidone, sodium starch glycolate by direct compression method. Nine formulations having superdisintegrants at different concentration levels were prepared. These tablets were evaluated for drug content, weight variation, friability, hardness, wetting time and disintegration time. Among all the formulations, F3 containing Ac-Di-Sol showed superior organoleptic properties along with excellent disintegration time and drug release. The percentage drug release of batch F3 showed 100.51% at the end of 16 minutes and emerged as best formulation. Hence it was concluded that superdisintegrants addition technique is useful for preparing orodispersible tablets by direct compression method.

G.Rajalakshmi *et al.*, (2010)[48] formulated Pheniramine maleate orodispersible tablets, a selective H1 receptor antagonist by direct compression method using superdisintegrants like croscarmellose sodium, crospovidone, sodium starch glycollate, low hydroxy propyl cellulose and pre gelatinized starch in different ratios. The blend was examined for various pre compression parameters. Tablets were evaluated by measuring hardness, friability, content uniformity, weight variation and

drug release pattern. All the tablets met the pharmacopoeial requirements for physical tests. The formulation with increase in concentration of superdisintegrants, showed rapid drug release. Stability studies were also perfomed. Dissolution studies indicated that the tablets containing crospovidone and croscarmellose sodium showed rapid dissolution compared to other disintegrants releasing almost 100% of the drug in six minutes.

Metker Vishal *et al.*, (2011)[49] developed mouth dissolving tablets of Lornoxicam using KYRON T-314 (Polacrillin Potassium) as a novel superdisintegrant. Mouth dissolving tablets of Lornoxicam were prepared by wet granulation technique using KYRON T-314 as superdisintegrant and menthol as subliming agent. The prepared tablets were evaluated for thickness, hardness, friability, weight variation, wetting time, *in vitro* dispersion time, drug content and *in vitro* dissolution study. All the evaluation parameters were found to be within the U.S.P limits. The formulation F5 prepared by direct sublimation of menthol showed 78.37% drug release at the end of 5 minutes when compared to other formulations. The formulation F5 was concluded as the best formulation. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Shailaja T *et al.*, (2012)[50] formulated and evaluated orodispersible tablets of Metoprolol tartrate with natural and synthetic superdisintegrants. The tablets were prepared by direct compression method using different ratio of natural superdisintegrant (agar, treated agar) and synthetic superdisintegrants (sodium starch glycolate, croscarmellose sodium and crospovidone) at concentrations ranging from 3%-12%. The blend of all formulations were evaluated for various precompression parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The prepared tablets were evaluated for various parameters like weight variation, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time, content uniformity and *in vitro* drug release. The formulation treated with agar have shown promising results compared to other formulation with semisynthetic superdisintegrants. The optimized formulation was subjected to stability studies for three months as per ICH guidelines. Disintegration times of formulations treated with agar were found to be in the range 3-19 seconds

and 95-100% drug release was observed in 5 minutes. The optimized formulation was found to be stable with insignificant change in the hardness, disintegration time, drug content and *in vitro* drug release.

Prasanth V V *et al.*, (2013)[51] developed oro dispersible tablets of Salbutamol sulphate using croscarmellose sodium, sodium starch glycolate, alginic acid, modified agar and modified guar gum as superdisintegrants. Precompression parameters were carried out to study the flow properties of powder to achieve uniformity of tablet weight and the values were found within the permissible limits. The tablets were prepared by direct compression method and possess a weight variation below ± 7.5%, hardness of 3.09 to 3.55 Kg/cm^2, percentage friability of 0.310 to 0.698, *in vitro* dispersion time of 22 to 54 seconds. The drug content uniformity was in between 95.94 to 99.67%, water absorption ratio 58.58 to 87.06%, wetting time 18 to 49.66 seconds and the *in vitro* drug release study showed more than 85% of the drug was released from all formulations within 15 minutes. Among all, formulation F12 was considered to be the best formulation which showed drug release upto 98.90% within 15 minutes and indicated rapid absorption, effective therapy and improved bioavailability.

Akula Nikhil Prashant *et al.*, (2015)[52] formulated oral disintegrating tablets of Nateglinide by direct compression method by the addition of superdisintegrants. Nine batches (F1-F9) of oral disintegrating tablets of Nateglinide were prepared by using superdisintegrants like crospovidone, croscromellose sodium and sodium starch glycolate in variable concentrations along with other excipents for the development of optimized formulation. All the formulations were subjected to evaluation studies like weight variation, hardness, friability, drug content, *in vitro* disintegration and *in vitro* dissolution studies and the results were found to be within the U.S.P limits. The formulation F8 was identified as best amongst all the other formulations and its release was found to be 91.78% within 35 minutes and it showed a constant release up to 45 minutes. The best formulation (F8) showed linearity when compared with marketed product. On the basis of the results, the formulation F8 containing crospovidone was considered as ideal among all other formulations used for the development of Nateglinide tablets.

T. Balakrishna *et al.*, (2016)[53] formulated Zolmitriptan orodispersible tablets using superdisintegrants such as croscarmellose sodium and crospovidone. The tablets were prepared by direct compression method. The compressed tablets were evaluated for postcompression parameters such as weight uniformity, hardness, friability, drug content and *in vitro* dissolution study. All the evaluation parameters were found to be within the U.S.P limits. Rapid release of Zolmitriptan from orodispersible tablets was observed which was influenced by the concentration of superdisintegrants. Among the various tablet formulations, F6 showed rapid drug release (99.8%) when compared to marketed formulation (84.89%) and emerged as best formulation.

G. Sandhyarani *et al.*, (2016) [54] formulated and evaluated orodispersible tablets of Domperidone by direct compression method. Seven formulations were prepared with different concentrations of superdisintegrants such as sodium starch glycolate, croscarmellose sodium and crospovidone. The prepared granules were evaluated for precompression parameters such as angle of repose, bulk density, compressibility index and Hausner's ratio. The formulated tablets were evaluated for thickness, hardness, weight variation, friability, drug content, water absorption ratio, wetting time, *in vitro* disintegration time and *in vitro* dissolution time. All the parameters were found to be within the acceptable limits. Formulation F5 (croscarmellose sodium + crospovidone) showed better water absorption ratio 76.73±2.88%, wetting time 26.66±2.08 seconds, disintegration time 25±1.0 seconds compared with other formulations and considered as better formulation.

A. Bharathi *et al.*, (2012)[55] formulated orally disintegrating tablets of Amlodipine Besylate by direct compression method using superdisintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate.. All the formulations were evaluated for pre compression, post compression parameters and the results were found to be within the U.S.P limits. Wetting time of formulations containing croscarmellose sodium was least and showed fast disintegration. Among the nine formulations studied, F9 showed short dispersion time with maximum drug realease (99.59%) in 20 minutes. The study concluded that combinations of superdisintegrants were found to be better in the formulation of fast dissolving tablets of Amlodipine Besylate rather than using alone.

S. Ramu *et al.*, (2014) [56] formulated and evaluated Valsartan mouth dissolving tablets by direct compression method. Total nine formulations were prepared by using various concentrations of superdisintegrants such as sodium starch glycolate, avicel pH102 and low HPC. The prepared tablets were evaluated for post compression parameters such as weight variation, hardness, friability, wetting time, *in vitro* dispersion time, drug content and *in vitro* dissolution studies. Formulations F1, F2, F3, released 89.83%, 91.10%, 96.20%, of drug respectively, Formulation F4, F5, and F6, released 85.11%, 88.71% and 90.44% respectively and formulation F7, F8, F9, released 78.26%, 82.26%, 85.31%, of drug respectively, at end of 15 minutes. Amongst all the formulations, Valsartan mouth dissolving tablets formulated by using sodium starch glycolate as superdisintegrant, showed good *in vitro* disintegration time (8.00 ± 1.023 sec), *in vitro* dispersion time (14.33 ± 1.24 sec), compared to other superdisintegrants. The optimized formulation (F3) containing sodium starch glycolate, as superdisintegrant showed best results compared to other formulations and emerged as the best formulation.

L. Divya *et al.*, (2014)[57] formulated Fluoxeitine hydrochloride oral dispersible tablets by three methods *viz* direct compression, wet granulation and sublimation method using superdisintegrants such as croscarmellose sodium and crospovidone. The prepared granules were evaluated for precompression parameters such as bulk density, tapped density, Hausner's ratio, compressibility index and angle of repose. The prepared tablets were evaluated for post compression parameters like hardness, friability, drug content, weight variation, disintegration time, wetting time, water absorption ratio, *in vitro* dispersion time and *in vitro* dissolution study. All the parameters were found to be with in the U.S.P limits. From the data obtained, it was observed that formulations with crospovidone as disintegrant exhibit quicker dispersion and wetting time compared to croscarmellose sodium. The percentage drug release was shown more in case of croscarmellose sodium than crospovidone. The formulation F6 containing combination of two superdisintegrants showed more percentage drug release (98%) at the end of 15 minutes than other formulations and emerged as best formulation.

Jain *et al.*, (2012)[58] formulated Oxcarbazepine oral disintegrating tablets by direct compression method using various ingredients like crospovidone, mannitol, sodium lauryl sulphate (SLS), magnesium stearate in different concentrations (5-10% 50%, 2-6%, 1 %). Chemical incompatibility studies confirmed that there was no interaction between drug and excipients used in the formulations. The tablets were evaluated for hardness, friability, weight variation, wetting time, water absorption ratio, assay and *in vitro* dissolution study. All the tablets were found to be within the U.S.P limits. The formulation F8 showed drug release of 98.05% at the end of 15 minutes and emerged as the best formulation.

P.Rohini *et al.*, (2014)[59] formulated orally disintegrating tablets of Rosuvastatin by direct compression technique. Fourteen batches were prepared using various superdisintegrants like sodium starch glycolate, croscarmellose sodium, Lycoat-RS720 and crospovidone in different concentrations. All the formulations were evaluated for weight variation, hardness, friability, *in vitro* disintegration time, drug content, wetting time and *in vitro* dissolution study. The results of all the tablets were found to be within the I.P limits. Among all the formulations, F13 (containing 8% of super disintegrants i.e. crospovidone and sodium starch glycolate (1:1) was considered to be the best formulation, which released upto 97% drug in 5 minutes. A comparative study of *in vitro* drug release was made with marketed product of Rosuvastatin which showed 93% drug release in one hour. The study concluded that the formulated tablets of Rosuvastatin containing crospovidone and sodium starch glycolate are better and effective than conventional tablets to meet patient compliance.

Bhupendra G *et al.*, (2010)[60] formulated orally disintegrating tablet of Cinnarizine by direct compression method. The superdisintegrants such as crospovidone, croscarmellose sodium and sodium starch glycolate were used. The prepared tablets were evaluated for weight variation, thickness, hardness, friability, taste, drug content, *in vitro* disintegrating time and *in vitro* drug release. Other parameters such as wetting time, water absorption ratio and drug-excipient compatibility were also evaluated. All the parameters were found to be within the I.P limits. Effect of varying concentrations of different superdisintegrants on disintegration time was studied. The formulation CP5 containing 6% crospovidone showed better drug release (95%) at the end of 15

minutes and disintegrating time (25 seconds). The drug release of formulation CP5 containing 6% crospovidone (CP5) when compared to the marketed conventional Cinnarizine tablet showed faster drug release and emerged as best formulation.

Kok khiang peh *et al.*, (2013)[61] briefed the emergence of orally disintegrating dosage forms as a breakthrough solution for non-compliance. Orally disintegrating dosage forms come in 2 types, namely orally disintegrating tablet (ODT) and orally disintegrating film (ODF). This article discussed the non-compliances issue in general, development of orally disintegrating dosage forms (ODT and ODF), their characteristics, advantages, formulation challenges, manufacturing methods, examples of patented technology of ODT, examples of ODF product, taste masking technologies, patients' acceptance and preference and lastly counseling.

Patel Kirtan kumar *et al.*, (2012)[62] formulated oro-dispersible tablets of Montelukast sodium using combination of the superdisintegrants and ludiflash by direct compression method. Three formulations having combination of superdisintegrants and three formulations having ludiflash at different concentration levels were prepared. The prepared tablets were evaluated for the post compression parameters such as hardness, friability, weight variation, wetting time, drug content, *in vitro* disintegration and *in vitro* dissolution study. All the parameters were found to be within the U.S.P limits. A rapid disintegration was observed for the formulation F6 containing 66.7% ludiflash. The *in vitro* dissolution profile indicated that among all the formulations, faster and maximum drug release was obtained from formulation F6 containing ludiflash and emerged as best formulation.

YashPaul *et al.*, (2011)[63] formulated taste masked dispersible tablets of Zidovudine by direct compression method using croscarmellose sodium (Ac-di-sol) as disintegrant. Surelease clear (E-7-19010) in concentration range of 0.044mL/tab to 0.052mL/tab completely masked the taste of Zidovudine. The prepared tablets were evaluated for general appearance, drug content, weight variation, thickness, hardness, friability, taste evaluation, mouth feel, *in vitro* dispersion time and *in vitro* dissolution studies. The results showed that all the parameters were found within the limits. Results also revealed that the tablets containing taste enhancers and surelease had a

good palatability. Oral dispersible tablets prepared using Surelease 0.044mL/tablet and Ac-di-sol 6% possessed least disintegration time (18.9 seconds), pleasant taste and offered better dissolution profile (98%) than all other dispersible tablet formulations and marketed conventional tablet formulation of Zidovudine.

Milind P Wagh *et al.*, (2010)[64] developed fast dissolving tablets of Aceclofenac by direct compression method after incorporating superdisintegrants croscarmellose sodium, crospovidone and sodium starch glycolate. Nine formulations having superdisintegrants at different concentration (10, 15, 20 mg) level were prepared and the effect of superdisintegrants on wetting time, dispersion time, drug content and *in vitro* release has been studied. Tablets containing croscarmellose sodium showed excellent *in vitro* dispersion time (23 minutes) and *in vitro* drug release (99.21% at the end of 30 minutes) as compared to other formulations. The results revealed that formulation F3 showed short dispersion time with maximum drug release in 30 minutes and emerged as best formulation.

Yogananda. R *et al.*, (2009)[65] formulated Piroxicam dispersible tablets by wet granulation and direct compression method using various natural disintegrating agents such as ispaghula husk, cassia tora and crosslinked tragacanth. The prepared tablets were evaluated for the post compression parameters such as hardness, friability, weight variation, wetting time, drug content, *in vitro* disintegration and *in vitro* dissolution study. All the parameters were found to be within the I.P limits. The study reveals that the formulation prepared by direct compression (F5) exhibits better dissolution rate (86%) at the end of 15 minutes and disintegration time (60 seconds) at low concentration of natural disintegrants. Hence the formulation F5 was selected as the best formulation.

S.B. Jadhav *et al.*, (2011)[66] formulated dispersible tablets of Diltiazem HCl using wet granulation method for enhanced patient compliance. Dispersible tablets were prepared using superdisintegrants such as croscarmellose sodium (Ac-Di-Sol) and sodium starch glycolate. All the formulations were evaluated for the post compression parameters of dispersible tablets. It was observed that all the formulations were acceptable with reasonable limits of standard required for dispersible tablets. Among

the formulations, batch A1 containing Ac-Di-Sol showed excellent *in vitro* disintegration time (35 seconds) and *in vitro* drug release (100%) as compared to other formulations and selected as best formulation. The study concluded that dispersible tablets with enhanced dissolution rate can be made using selected superdisintegrants.

Radha Rani Earl *et al.*,(2016)[67] prepared fast dissolving tablets of Diclofenac sodium using 3 different superdisintegrants like sodium starch glycolate, croscarmellose sodium and crospovidone by direct compression technique. The precompression parameters of the prepared tablet blend like angle of repose, bulk density, tapped density, carr's index, Hausner's ratio and the post compression parameters like hardness, friability, weight variation, *in vitro* dispersion time, wetting time, water absorption ratio, *in vitro* disintegration time and *in vitro* drug dissolution were evaluated. All the parameters were found to be within the I.P limits. It was concluded that formulation F10 containing crospovidone showed better release 97.7% at the end of 20 minutes and emerged as best formulation.

K. Gnanaprakash *et al.*, (2009)[68] developed fast dissolving tablets of Valdecoxib by direct compression method. The fast dissolving tablets of Valdecoxib was prepared with some carriers (polymers) and superdisintegrants such as polyvinyl pyrrolidone (PVP), sodiumcarboxy methyl cellulose (SCMC), crospovidone NF and β – Cyclodextrin. The above mentioned carriers and superdisintegrants were taken in different proportions of 5, 10 and 15%. The blend was examined for Angle of repose, bulk density, compressibility index and Hausner's ratio. The prepared tablets were evaluated for hardness, drug content uniformity, friability, *in vitro* disintegration time and *in vitro* dissolution rate. All the parameters were found to be within the I.P limits. The formulation F9 containing crospovidone showed maximum drug release of 99.88% at the end of 10 minutes and emerged as the best formulation and the drug release was found to be comparable with the marketed dispersible tablet of Valdecoxib.

Snehal T Hase *et al.*, (2015)[69] developed mouth dissolving tablets of Pioglitazone HCl using superdisintegrants such as sodium starch glycolate and crospovidone by direct compression technique. The tablets were evaluated for weight variation, hardness, percentage friability, wetting time and disintegration time. Eight formulations having superdisintegrants in different concentration levels were prepared to access their efficiency and critical concentration level. Tablets containing sodium starch glycolate along with crospovidone (F5) showed excellent disintegration time (52 seconds) and *in vitro* drug release 98.9% at the end of 25 minutes compared to other formulations and was selected as better formulation.

Bhaskar Umarji *et al.*, (2012)[70] formulated fast dissolving tablets of Levocetrizine HCl using sodium starch glycolate, croscarmellose sodium and crospovidone as superdisintegrants by direct compression method. The tablets prepared were evaluated for various parameters like weight variation, hardness, friability, *in vitro* dispersion time, drug content, wetting time, *in vitro* drug release, FT-IR and XRD studies. The tablets prepared by direct compression method possess weight variation below ±7.5%, hardness of 3 to 4.0 Kg/cm², percentage friability of 0.51 to 0.85 %, *in vitro* dispersion time of 17 to 58 seconds, wetting time of 13 to 48 seconds and *in vitro* drug release of 94 % to 99 % within 20 minutes. The formulation (MD6) containing crospovidone and sodium starch glycolate showed better disintegration time and 99% drug release within 20 minutes and emerged as best formulation.

CHAPTER-3

Aim and Plan of Work

CHAPTER – 3

AIM AND PLAN OF WORK

3.1 AIM AND OBJECTIVE OF WORK

- The aim of the present study is to design and evaluate the orally disintegrating tablets of Ondansetron hydrochloride using various superdisintegrants and compare with marketed Ondansetron hydrochloride dispersible tablets.

- The main problem encountered with common oral dosage forms is that they have to be swallowed along with water and during the travel or if drinking water is not available or for dysphagic patients, it is difficult to administer these drugs and hence it is beneficial to administer such drugs as orally disintegrating tablets. Moreover patients finding difficult to swallow these tablets, especially elders and pediatrics do not comply with prescription, which results in patient noncompliance.

- Thus ODT^S are beneficial to patients who find it difficult to swallow tablets and moreover some of the drugs which are soluble in saliva are absorbed from the mouth, pharynx and oesophagus thereby avoiding first pass metabolism which enhances bioavailability of the drug.

The objective of the work is to prevent inherent drawbacks associated with conventional tablets such as risk of choking, bitter taste and difficult in swallowing by formulating orally disintegrating tablets of Ondansetron HCl there by providing faster disintegration and rapid release, bypassing first pass effect, improved patient compliance and therapeutic effectiveness.

3.2 PLAN OF WORK

The present work was carried out to formulate orally disintegrating tablets of Ondansetron hydrochloride and to evaluate the tablets for various parameters. It was planned to carry out this work as outlined below.

1. To carry out the preformulation studies of API such as
    - ✓ Organoleptic properties
    - ✓ Solubility
2. To carry out the drug and excipient compatibility study by FT-IR.
3. To carry out the pre-compression parameters of the powder blend such as
    - ✓ Angle of repose
    - ✓ Bulk density
    - ✓ Tapped density
    - ✓ Compressibility index
    - ✓ Hausner's ratio
4. To formulate orally disintegrating tablets of Ondansetron HCl by "Direct compression method" using various superdisintegrants such as crospovidone, sodium starch glycolate and croscarmellose sodium.
5. To evaluate the compressed tablets for following parameters such as
    - ✓ Hardness
    - ✓ Thickness
    - ✓ Friability
    - ✓ Weight variation
    - ✓ Wetting time
    - ✓ Water absorption ratio
    - ✓ *In vitro* dispersion test
    - ✓ Disintegration time
    - ✓ Fineness of dispersion
    - ✓ Assay
    - ✓ *In vitro* release studies
6. To perform stability study for the best formulation at 25^0C ±2 /60% ±5%RH and 40^0 C ±2 /75% ±5%RH for 3 months.

CHAPTER-4

Materials and Methods

List of Materials

CHAPTER - 4

MATERIALS AND METHODS

4.1. MATERIALS USED AND MANUFACTURERS

Table: 4 List of Materials used and Manufacturers

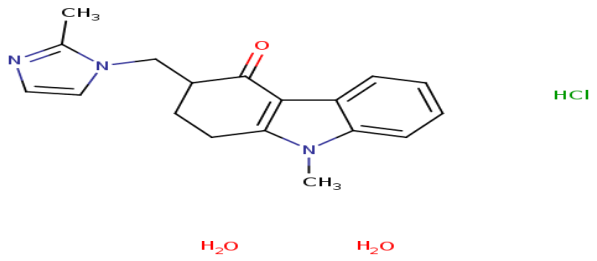
S.No	Materials	Manufacturers
1	Ondansetron hydrochloride	Mahrshee Laboratories Pvt. Ltd, Gujarat.
2	Microcrystalline cellulose	NB Entrepreneurs, Nagpur.
3	Mannitol	Qingdao Bright Moon Seaweed Group Co. Ltd, China.
4	Sorbitol	Gujarat Ambuja Exports Ltd, Ahmedabad.
5	Croscarmellose sodium	JR Pharma, Gujarat.
6	Crospovidone	Boai NKY Pharmaceuticals Ltd, China.
7	Sodium starch glycolate	Maruti Chemicals, Ahmedabad.
8	Methyl paraben	Rasula Pharmaceuticals and Fine Chemicals, Hyderabad.
9	Propyl paraben	Rasula Pharmaceuticals and Fine Chemicals, Hyderabad.
10	Sucralose	The Nutrasweet Co, USA.
11	Sunset yellow	Neelikon Food Dyes and Chemicals Limited, Mumbai.
12	Strawberry flavor	IFF India Pvt. Ltd, Chennai.
13	Magnesium stearate	Par Drugs and Chemicals Pvt. Ltd, Vadodara.

Drug Profile

4.2 DRUG PROFILE

DRUG[71] : Ondansetron hydrochloride

STRUCTURAL FORMULA :



MOLECULAR FORMULA : $C_{18}H_{19}N_3O.HCl.\ 2H_2O.$

MOLECULAR WEIGHT : 365.90 g/mol.

CHEMICAL NAME : 9-methyl-3-[(2-methylimidazol-1-yl)methyl]-2,3 dihydro-1H-carbazol-4-one; dihydrate; hydrochloride.

CATEGORY : A competitive serotonin 5-HT_3 receptor antagonist.

pH : 4.5-4.6.

DESCRIPTION : A white or almost white powder.

SOLUBILITY : It is sparingly soluble in water and in ethanol; soluble in methanol.

MELTING POINT : 231-232°C.

DOSE : 4mg, 8mg tablets twice a day for 3-5 days, 2mg/ml -2ml, 4ml i.v injections ½ an hr before chemotherapeutic infusion.

PHARMACOKINETICS[72]

Ondansetron is absorbed from the gastrointestinal tract and undergoes some first pass metabolism. Volume of distribution of Ondansetron is 160 ltr. Plasma protein binding of Ondansetron is 70-76%. Mean bioavailability in healthy subjects, following administration of a single 4 mg tablet, is approximately 56%. Peak plasma concentration occurs 1.5 hours after oral administration. Extensively metabolized by hepatic cytochrome P450 2D6 isozyme to 9-hydroxyisperidone. Biological half-life is 5-7 hrs. Excretion via urine; 44-60% as metabolites, 5-10% as unchanged, faeces (approximately 25%).

MECHANISM OF ACTION[73]

Ondansetron is a selective serotonin 5-HT_3 receptor antagonist. The antiemetic activity of the drug is brought through the inhibition of 5-HT_3 receptors present both centrally (medullary chemoreceptor zone) and peripherally (GI tract). This inhibition of 5-HT_3 receptors in turn inhibits the visceral afferent stimulation of the vomiting center, likely indirectly at the level of the area postrema, as well as through direct inhibition of serotonin activity within the area postrema and the chemoreceptor trigger zone.

INDICATIONS[74]

Ondansetron HCl is used for the prevention of nausea and vomiting associated with the following conditions

- Chemotherapy induced nausea and vomiting
- Cholestatic pruritus
- Post-operative nausea and vomiting (PONV)
- Uremic pruritus
- Radiation induced nausea and vomiting

TOXICITY

Low blood pressure, fainting, sudden blindness and severe constipation.

DOSAGE AND ADMINISTRATION[75]

Adult: 8 mg b.i.d, for up to 5 days after the end of a course of chemotherapy.

Child: 4-11 year 4 mg 30 minutes prior to chemotherapy; repeat dose at 4 and 8^{th} hr after initial dose, then 4 mg t.i.d for 1 to 2 days after completion of chemotherapy.

Elderly: No dose adjustment needed.

DRUG INTERACTIONS[76]

CYP3A4 inducers (eg, Phenytoin, Carbamazepine and Rifampicin) may reduce the plasma levels of Ondansetron thereby decreasing the antiemetic effect. Concomitant use of Tramadol may result in reduced analgesic activity of Tramadol.

CONTRAINDICATIONS

The concomitant use of Apomorphine with Ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness. Ondansetron tablets are contraindicated for patients known to have hypersensitivity to the drug.

ADVERSE REACTIONS

Central Nervous System	**:**	Headache, sedation, dizziness, anxiety.
Dermatologic	**:**	Pruritus, rash, flushing, urticaria.
Gastro Intestinal Tract	**:**	Constipation, diarrhea, dry mouth, abdominal pain.
Respiratory Tract	**:**	Hypoxia, bronchospasm.

MARKETED PRODUCTS[77]

Avetron-MD 4mg, Egatron-4 4mg, Vomicard-MD 4mg, Estaset 4 mg, Ondaris syrup, Northstar oral solution, Nvest syrup, Vondan injection, Ondax injection.

Excipient Profile

4.3. EXCIPIENTS PROFILE

4.3.1. MANNITOL[78]

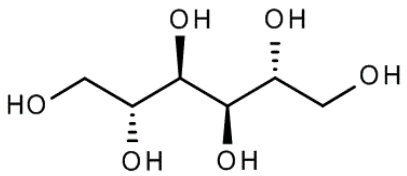
NON-PROPRIETARY NAMES : BP: Mannitol.
JP: D-Mannitol.
PhEur: Mannitol.
USP: Mannitol.

SYNONYMS : Cordycepic acid, Emprove, Manna sugar, Pearlitol, D-mannite, Mannite, Mannitolum, Mannogem.

CHEMICAL NAME : D-Mannitol.

EMPIRICAL FORMULA : $C_6H_{14}O_6$.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 182.17g/mol.

MELTING POINT : 166-168°C.

SOLUBILITY : Soluble in alkalis and practically insoluble in ether.

DESCRIPTION : Mannitol occurs as a white, odorless, crystalline powder or free-flowing granules.

FUNCTIONAL CATEGORY	**:**	Diluent, plasticizer, sweetening agent, tablet and capsule diluent, therapeutic agent and tonicity agent.
APPLICATIONS	**:**	Mannitol is widely used in Pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations. Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available and also used in wet granulation method.
STABILITY AND STORAGE CONDITIONS	**:**	Mannitol is stable in the dry state and in aqueous solutions. The bulk material should be stored in a well-closed container in a cool, dry place.
INCOMPATIBILITIES	**:**	Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic.

4.3.2. SORBITOL

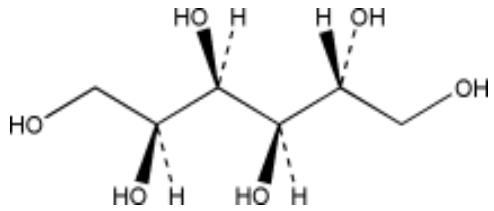
NON-PROPRIETARY NAMES[78] **:** BP: Sorbitol.
JP: D-Sorbitol.
PhEur: Sorbitolum.
USP-NF: Sorbitol.

SYNONYMS **:** 1,2,3,4,5,6-hexanehexol, Liponic 70-NC, Meritol, Neosorb, Sorbite, D-sorbitol, Sorbitol Instant, Sorbogem.

CHEMICAL NAME **:** D- Glucitol.

EMPIRICAL FORMULA **:** $C_6H_{14}O_6$.

MOLECULAR STRUCTURE **:**



MOLECULAR WEIGHT[79] **:** 182.17 g/mol.

MELTING POINT **:** 110–112^{o} C.

SOLUBILITY **:** Practically insoluble in chloroform and ether, slightly soluble in methanol.

DESCRIPTION **:** Sorbitol is D- glucitol. It is a hexahydric alcohol related to mannose and is isomeric with mannitol. Sorbitol occurs as an odorless, white or almost colorless, crystalline, hygroscopic powder.

FUNCTIONAL CATEGORY **:** Humectant, plasticizer, sweetening agent, tablet and capsule diluent.

APPLICATIONS : Sorbitol is widely used as an excipient in pharmaceutical formulations. It is also used extensively in cosmetics and food products. It is particularly useful in chewable tablets owing to its pleasant, sweet taste and cooling sensation.

STABILITY AND STORAGE CONDITIONS : Sorbitol is stable in air, dilute acids and alkalis. The bulk material is hygroscopic and should be stored in an airtight container in a cool, dry place.

INCOMPATIBILITIES : Sorbitol will form water-soluble chelates with many divalent and trivalent metal ions in strongly acidic and alkaline conditions. Addition of liquid polyethylene glycols to sorbitol solution, with vigorous agitation, produces a waxy, water-soluble gel with a melting point of 35–40^{O}C. Sorbitol solutions also react with iron oxide to become discolored. Sorbitol increases the degradation rate of Penicillins in neutral and aqueous solutions.

4.3.3. MICROCRYSTALLINE CELLULOSE[80]

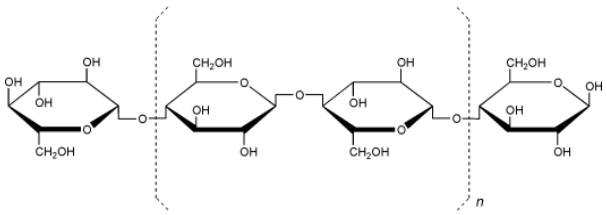
NON-PROPRIETARY NAMES : BP: Microcrystalline cellulose.
JP: Microcrystalline cellulose.
PhEur: Cellulosum microcrystallinum.
USP-NF: Microcrystalline cellulose.

SYNONYMS : Avicel PH, Cellulose gel, Celphere, Crystalline cellulose, Emcocel, Ethispheres, Fibrocel, Pharmacel.

CHEMICAL NAME : Cellulose.

EMPIRICAL FORMULA : $(C_6H_{10}O_5)_n$.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : Approximately 36000.

MELTING POINT[78] : Melts at 260- 270^{0}C.

SOLUBILITY : Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids and most organic solvents.

DESCRIPTION	**:**	Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.
FUNCTIONAL CATEGORY	**:**	Adsorbent, suspending agent, diluent and tablet disintegrant.
APPLICATIONS	**:**	Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.
STABILITY AND STORAGE CONDITIONS	**:**	It should be stored at room temperature in well-closed containers under dry and odor- free conditions.
INCOMPATIBILITIES	**:**	Microcrystalline cellulose is incompatible with strong oxidizing agents.

4.3.4. SODIUM STARCH GLYCOLATE[81]

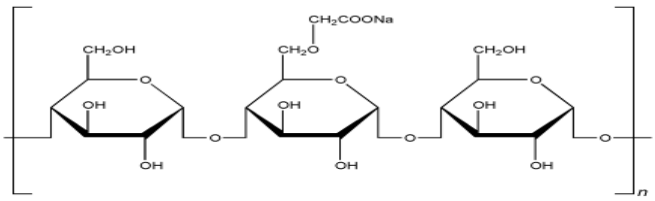
NON-PROPRIETARY NAMES : BP: Sodium starch glycolate.
PhEur: Carboxy methylamylum natricum.
USP-NF: Sodium starch glycolate.

SYNONYMS : Carboxymethyl starch, Sodium salt, Explosol, Glycolys, Primojel, Starch carboxymethyl ether.

CHEMICAL NAME : Sodium carboxy methyl starch.

EMPIRICAL FORMULA : $C_2H_4O_3$.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 98.033 g/mol.

MELTING POINT : Does not melt but chars at 200^{o}C.

SOLUBILITY[78] : Sparingly soluble in ethanol (95%), practically insoluble in water.

DESCRIPTION : Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder.

FUNCTIONAL CATEGORY : Tablet and capsule disintegrant.

APPLICATIONS : Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

STABILITY AND STORAGE CONDITIONS : Sodium starch glycolate is stable and should be stored in a well closed container to protect it from wide variations in humidity and temperature that may cause caking.

INCOMPATIBILITIES : Sodium starch glycolate is incompatible with ascorbic acid.

4.3.5. CROSCARMELLOSE SODIUM[82]

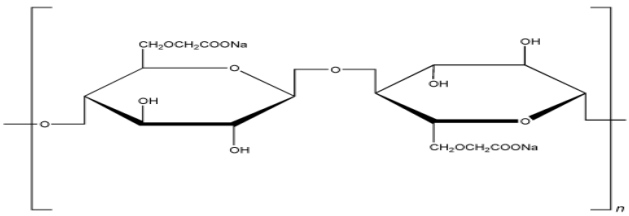
NON-PROPRIETARY NAMES : BP: Croscarmellose sodium.
PhEur: Croscarmellose sodium.
USP-NF: Croscarmellose sodium.

SYNONYMS : Ac-Di-Sol, Crosslinked carboxy methylcellulose sodium, Modified cellulose gum, Primellose, Solutab, Vivasol.

CHEMICAL NAME : Carboxymethyl ether, Sodium salt crosslinked.

EMPIRICAL FORMULA : $C_{28}H_{30}Na_8O_{27}$.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 90,000–700,000.

MELTING POINT : More than 205^0C.

SOLUBILITY [78] : Insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

DESCRIPTION : Croscarmellose sodium occurs as an odorless, white colored powder.

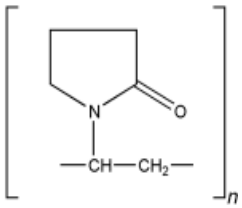
FUNCTIONAL CATEGORY : Tablet and capsule disintegrant.

APPLICATIONS : Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

STABILITY AND STORAGE CONDITIONS : Croscarmellose sodium is a stable though hygroscopic material. It should be stored in well closed container.

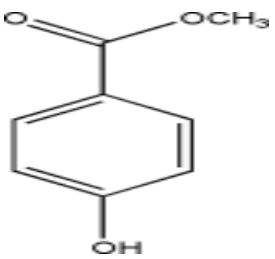
INCOMPATIBILITIES : The efficacy of croscarmellose sodium may be slightly reduced in tablet formulations prepared by either wet granulation or direct compression process which contains hygroscopic excipients such as sorbitol.

4.3.6. CROSPOVIDONE[83]

NON-PROPRIETARY NAMES	**:**	BP: Crospovidone. PhEur: Crospovidonum. USP-NF: Crospovidone.
SYNONYMS	**:**	Crosslinked povidone, Kollidon CL, Kollidon CL-M, Polyplasdone XL, Polyvinylpolypyrrolidone.
CHEMICAL NAME	**:**	1-Ethenyl-2-pyrrolidinone homopolymer.
EMPIRICAL FORMULA	**:**	$(C_6H_9NO)_n$.
MOLECULAR STRUCTURE	**:**	
MOLECULAR WEIGHT	**:**	2.5 g/mol.
MELTING POINT	**:**	150^0C.
SOLUBILITY	**:**	Practically insoluble in water and most common organic solvents.
DESCRIPTION	**:**	Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

FUNCTIONAL CATEGORY	**:**	Tablet disintegrant.
APPLICATIONS [78]	**:**	Crospovidone is used as tablet disintegrant at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. Crospovidone can also be used as a solubility enhancer.
STABILITY AND STORAGE CONDITIONS	**:**	Crospovidone is a hygroscopic material. So it should be stored in an airtight container in a cool, dry place.
INCOMPATIBILITIES	**:**	Crospovidone is compatible with most organic and inorganic Pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

4.3.7. METHYL PARABEN[84]

NON-PROPRIETARY NAMES	**:**	BP: Methyl hydroxybenzoate. JP: Methyl parahydroxybenzoate. PhEur: Methyl parahydroxybenzoate. USP-NF: Methylparaben.
SYNONYMS	**:**	4-Hydroxybenzoic acid methyl ester, Methyl p-hydroxybenzoate, Nipagin M.
CHEMICAL NAME	**:**	Methyl-4-hydroxy benzoate.
EMPIRICAL FORMULA	**:**	$C_8H_8O_3$.
MOLECULAR STRUCTURE	**:**	
MOLECULAR WEIGHT	**:**	152.15 g/mol.
MELTING POINT	**:**	125–128^0 C.
SOLUBILITY	**:**	Soluble in acetone, alcohol and in water when heated.
DESCRIPTION	**:**	Methylparaben occurs as colorless crystals or a white crystalline powder. It is odorless or almost odorless and has a slight burning taste.

FUNCTIONAL CATEGORY	**:**	Antimicrobial preservative.
APPLICATIONS[78]	**:**	Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products and pharmaceutical formulations.
STABILITY AND STORAGE CONDITIONS	**:**	Aqueous solutions of methylparaben at pH 3–6 may be sterilized by autoclaving at 120^0C for 20 minutes, without decomposition. Methylparaben should be stored in a well-closed container in a cool, dry place.
INCOMPATIBILITIES	**:**	The antimicrobial activity of methylparaben is considerably reduced in the presence of nonionic surfactants, such as polysorbate 80, as a result of micellization. Methylparaben is discolored in the presence of iron and is subjected to hydrolysis by weak alkalis and strong acids.

4.3.8. PROPYL PARABEN[85]

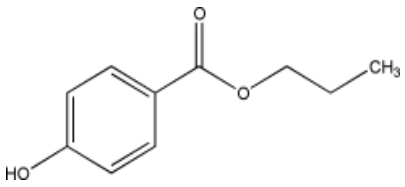
NON-PROPRIETARY NAMES : BP: Propyl hydroxybenzoate.
JP: Propyl parahydroxybenzoate.
PhEur: Propyl parahydroxybenzoate.
USP-NF: Propylparaben.

SYNONYMS : 4-Hydroxybenzoic acid propyl ester, Nipasol M, Propyl p-hydroxybenzoate, Propyl parasept, Solbrol P.

CHEMICAL NAME : Propyl 4-hydroxybenzoate.

EMPIRICAL FORMULA : $C_{10}H_{12}O_3$.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 180.20 g/mol.

MELTING POINT : 96-99^{o}C.

SOLUBILITY : Soluble in acetone, alcohol and in water when heated.

DESCRIPTION : Propylparaben occurs as a white, crystalline, odorless and tasteless powder.

FUNCTIONAL CATEGORY	**:**	Antimicrobial preservative.
APPLICATIONS[78]	**:**	Propylparaben is widely used as an antimicrobial preservative in cosmetics, food products and Pharmaceutical formulations.
STABILITY AND STORAGE CONDITIONS	**:**	Propylparaben is stable under normal conditions and decomposes on heating. It should be stored in a tightly closed container.
INCOMPATIBILITIES	**:**	The activity of propylparaben can be adversely affected by the presence of other excipients or active ingredients, such as atropine, essential oils, iron, magnesium trisilicate, talc, polysorbate and other nonionic surfactants, sorbitol, weak alkalis and strong acids.

4.3.9. SUCRALOSE[78]

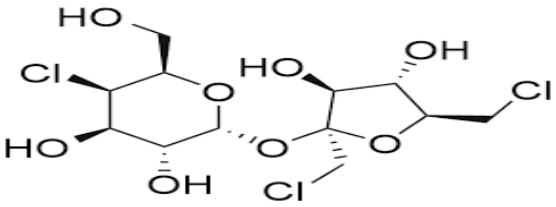
NON-PROPRIETARY NAMES : USP-NF: Sucralose.

SYNONYMS : Sucralose, Sucralosum, Sucra plus.

CHEMICAL NAME : 1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl -4-chloro-4-deoxy-α-D-galactopyranoside.

EMPIRICAL FORMULA : $C_{12}H_{19}C_{l3}O_{8.}$

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 397.64 g/mol.

MELTING POINT : 130^0C.

SOLUBILITY : Freely soluble in ethanol (95%), methanol and water. Slightly soluble in ethyl acetate.

DESCRIPTION : Sucralose is a white to off-white colored, free-flowing, crystalline powder.

FUNCTIONAL CATEGORY : Sweetening agent.

APPLICATIONS : Sucralose is used as a sweetening agent in beverages, foods and Pharmaceutical applications.

STABILITY AND STORAGE CONDITIONS : Sucralose is a relatively stable material. In aqueous solution, at highly acidic conditions (pH < 3) and at high temperature, it is hydrolyzed to a limited extent, producing 4-chloro-4-deoxygalactose and 1,6-dichloro-1,6-dideoxyfructose. It should be stored in a well closed container in a cool, dry place, at a temperature of not exceeding 21^0C.

INCOMPATIBILITIES : It alters process in the gut, this can limit the absorption and thus the effectiveness of life-saving therapeutic drugs, including the drugs used for cancer and heart disease.

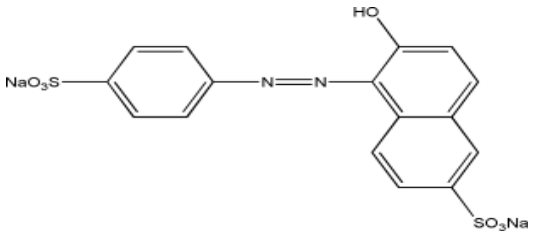
4.3.10. SUNSET YELLOW FCF[86]

SYNONYMS : Orange yellow S, FD& C yellow, E110.

CHEMICAL NAME : Disodium 6-hydroxy-5-[(4-sulfophenyl) azo]-2-naphthalenesulfonate.

EMPIRICAL FORMULA : $C_{16}H_{10}N_2Na_2O_7S_2$.

MOLECULAR STRUCTURE :



MOLECULAR WEIGHT : 452.37 g/mol.

MELTING POINT : 300^0C.

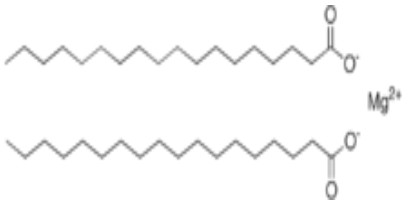
SOLUBILITY : Soluble in water, sparingly soluble in ethanol.

DESCRIPTION : Reddish yellow powder. Aqueous solutions are bright orange colored.

FUNCTIONAL CATEGORY : Coloring agent.

APPLICATIONS[87]	**:**	Sunset yellow is used as coloring agent in food, cosmetics and pharmaceuticals. For example, it is used in candy, desserts, snacks, sauces and preserved fruits. Sunset yellow is often used in conjunction with E123, amaranth to produce a brown color in both chocolates and caramel.
STABILITY AND STORAGE CONDITIONS	**:**	Sunset yellow is sensitive to light. So it should be stored at room temperature in a well closed light resistant container.
INCOMPATIBILITIES	**:**	It is poorly compatible with citric acid, saccharose solutions and saturated sodium bicarbonate solutions. Incompatible with ascorbic acid, gelatin and glucose.

4.3.11. MAGNESIUM STEARATE[78]

NON-PROPRIETARY NAMES	**:**	BP: Magnesium stearate. JP: Magnesium stearate. PhEur: Magnesii stearas. USP-NF: Magnesium stearate.
SYNONYMS	**:**	Magnesium octadecanoate, Octadecanoic acid, Stearic acid and Magnesium salt.
CHEMICAL NAME	**:**	Octadecanoic acid magnesium salt.
EMPIRICAL FORMULA	**:**	$C_{36}H_{70}MgO_4$.
MOLECULAR STRUCTURE	**:**	
MOLECULAR WEIGHT	**:**	591.34 g/mol.
MELTING POINT	**:**	117-150^{0}C.
SOLUBILITY	**:**	Practically insoluble in ethanol, ether and waters. Slightly soluble in warm benzene and warm ethanol.
DESCRIPTION	**:**	Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor and a characteristic taste.

FUNCTIONAL CATEGORY	**:**	Tablet and capsule lubricant.
APPLICATIONS	**:**	Magnesium stearate is widely used in cosmetics, foods and Pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at a concentration between 0.25% and 5.0% w/w. It is also used in barrier creams.
STABILITY AND STORAGE CONDITIONS	**:**	Magnesium stearate is stable under ordinary conditions. It should be stored in a well closed container in a cool dry place.
INCOMPATIBILITIES	**:**	It is incompatible with strong acids, alkalis and iron salts. It cannot be used in products containing aspirin, vitamins and alkaloidal salts.

List of Instruments

4.4. INSTRUMENTS USED AND MANUFACTURERS

Table: 5 List of Instruments used and Manufacturers

S. No.	Instruments	Manufacturers
1	Single pan Electronic Balance	Sartorius AG, Germany.
2	12 Station D/B Tooling Compression Machine	Fluid Pack, Ahmedabad.
3	Vernier Caliper	Mitutoyo Corporation, Japan.
4	Dissolution Test Apparatus	Electro Lab India Pvt. Ltd, Mumbai.
5	Hardness Tester	Campbell Electronics, Mumbai.
6	Friability Test Apparatus	Electro Lab India Pvt. Ltd, Mumbai.
7	Standard Sieves	Jayant Scientific Industries, Mumbai.
8	Disintegration Test Apparatus	Electro Lab India Pvt. Ltd, Mumbai.
9	FT-IR Spectrophotometer	Shimadzu, Japan.
10	HPLC	Waters Corporation, USA.
11	Stability Chamber	Labtop House, Mumbai.
12	Blister Packing Machine	Elmach Packages Pvt. Ltd, Mumbai.

Methodology

4.5. METHODOLOGY

4.5.1. CALIBRATION CURVE OF ONDANSETRON HYDROCHLORIDE[88]

Preparation of 0.1M Hydrochloric Acid

Place 8.5 ml of concentrated hydrochloric acid into the 1000 ml volumetric flask and the volume were made up with de-mineralized water.

Preparation of Mobile Phase

0.05 M Potassium dihydrogen phosphate buffer (pH 4.5 ± 0.05): Acetonitrile: Methanol were mixed in the ratio of 50:40:10.

Calibration Curve of Ondansetron Hydrochloride

100 mg of Ondansetron hydrochloride was dissolved in 100ml of 0.1M hydrochloric acid and further dilutions were made using the same solution to obtain concentrations ranging from 1µg/ml to 10µg/ml. The peak areas of the each dilutions were measured at 248 nm by HPLC method. The obtained peak areas against each dilution levels are shown in Table: 6 and the concentration versus peak area is plotted in a graph which is shown in Fig: 5.

Table: 6 Standard Calibration Curve Data of Ondansetron Hydrochloride

S.NO.	Concentration (µg/*ml*)	Peak Area (mAU)
1	1	241310
2	2	482580
3	3	723910
4	4	965260
5	5	1206590
6	6	1447860
7	7	1689178
8	8	1930480
9	9	2171800
10	10	2413100

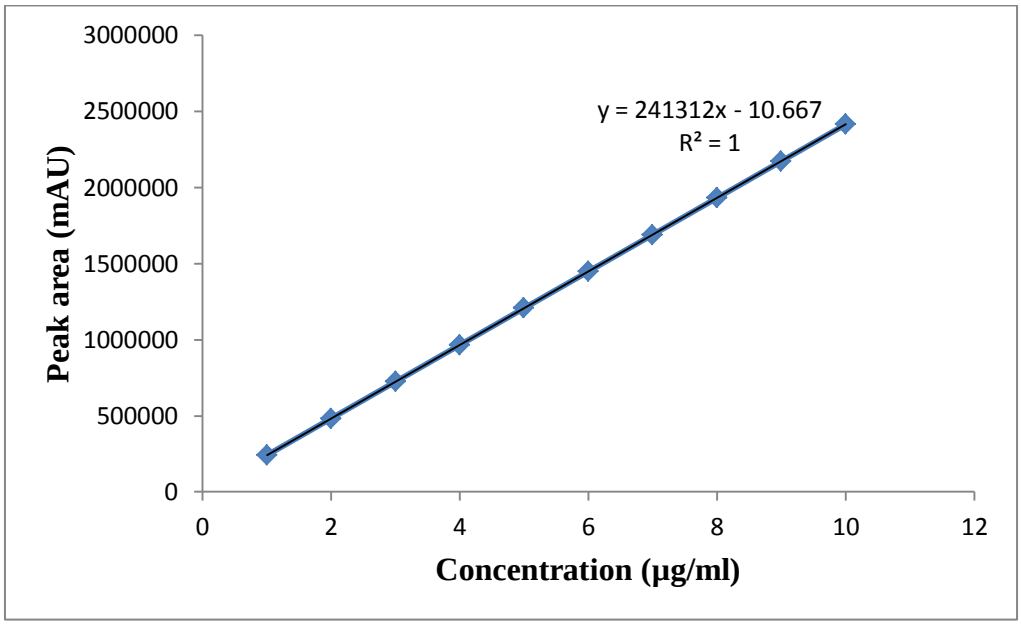


Fig: 5 Standard Calibration Curve of Ondansetron Hydrochloride

4.5.2. PREFORMULATION STUDIES[89]

Preformulation can be defined as an investigation of physical and chemical properties of drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms. The use of preformulation parameters maximizes the chances in formulating acceptable, safe, efficacious and stable product.

4.5.2.1. ORGANOLEPTIC PROPERTIES

The organoleptic properties like color, odor and taste of the API was evaluated.

a) Color: A small quantity of Ondansetron HCl was taken in a butter paper and viewed in well-illuminated place.

b) Taste and odor: Very less quantity of Ondansetron HCl was used to assess the taste with the help of tongue as well as smelled to get odor.

4.5.2.2. SOLUBILITY TEST[90]

Solubility of Ondansetron hydrochloride in water, methanol and ethanol was determined by using Sonicator at room temperature. Approximate solubility of drugs as per B.P was indicated in table: 7.

Table: 7. Solubility Specification of Drugs

Solubility	Approximate Volume of Solvent in ml per gm of Solute
Very soluble	Less than 1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10000
Practically insoluble/ Insoluble	More than 10000

4.5.2.3. DRUG: EXCIPIENT COMPATIBILITY STUDIES

Compatibility studies were performed by preparing blend of different excipients with drug and stored at $40^{O}C \pm 2^{O}C$ /75±5%RH for one month. The blend were evaluated for every 15 days for changes like caking, liquefaction, discoloration and odor formation. The drug excipient compatibility studies were shown in table: 8.

Table: 8 Drug : Excipients Compatibility Protocol

S. No.	Drug and Excipients	Ratio (Drug:Excipient)
1	Ondansetron HCl	1
2	Ondansetron HCl + Mannitol (anhydrous)	1:1
3	Ondansetron HCl + Sorbitol (granular grade)	1:1
4	Ondansetron HCl + Microcrystalline cellulose (MCC-112)	1:1
5	Ondansetron HCl + Sodium starch glycolate	1:1
6	Ondansetron HCl + Croscarmellose sodium	1:1
7	Ondansetron HCl + Crospovidone	1:1
8	Ondansetron HCl + Methylparaben	1:1
9	Ondansetron HCl + Propylparaben	1:1
10	Ondansetron HCl + Sucralose	1:1
11	Ondansetron HCl + Sunset yellow FCF	1:0.5
12	Ondansetron HCl + Strawberry flavor	1:0.5
13	Ondansetron HCl + Magnesium stearate	1:1

4.5.3. FT-IR STUDIES[91]

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100 mg of this mixture was compressed to form a transparent pellet using a hydraulic press at 10 tons pressure. It was scanned between 4000- 500 cm^{-1} in a shimadzu FT-IR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

4.5.4. EVALUATION OF PRECOMPRESSION PARAMETERS

4.5.4.1. MICROMERITIC PROPERTIES

4.5.4.1.1. ANGLE OF REPOSE[92, 93]

Angle of repose is defined as the maximum angle that can be obtained between the surface of a powder heap and the horizontal plane. Angle of repose has been used as an indirect method of quantifying powder flowability, because of their relationship with interparticle cohesion.

The angle of repose was determined by funnel method. The funnel was fixed at a particular height 'h' on a burette stand. A graph paper was placed below the funnel on the table. The powder blend whose angle of repose is to be determined was passed slowly through the funnel, until if forms a pile. Further addition of powder blend was stopped as soon as the pile touches the tip of the funnel. Circumference of the pile of powder blend was drawn with a pencil without disturbing the pile. The radius of the pile 'r' was noted. Flow properties and corresponding angle of repose as per I.P Table: 9. Angle of repose of the powder blend was calculated by using the following formula,

$$\tan\theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where,

θ = Angle of repose

h = Height of the pile.

r = Radius of the pile.

Table: 9 Flow Properties and Corresponding Angle of Repose as per I.P

Flow Property	Angle of Repose
Excellent	25 – 30
Good	31 – 35
Fair	36 – 40
Passable	41 – 45
Poor	46 – 55
Very poor	56 – 65
Very very poor	> 66

4.5.4.1.2. BULK DENSITY[94, 95]

Bulk density is defined as powder mass divided by its bulk volume without any tapping. Powder bulk density depends primarily on particle size distribution, particle shape and the tendency of particles adhere to each other. Some particles may pack loosely, leading to fluffy and light weight powder, while others may contain smaller particles that sift between larger particles to fill the void, leading to dense and heavy powder. Bulk density is often used to calculate the batch size for blender and granulator.

Weighed quantity of powder blend from each formulation was taken in a 50 ml measuring cylinder and the initial volume of the powder blend in the measuring cylinder was noted. Bulk density of the powder blend was calculated by using the formula,

$$\rho_b = M / V_b$$

Where,

ρ_b = Bulk density,

M = Weight of the sample in gm,

V_b = Final volume of the powder blend in cm^3.

4.5.4.1.3. TAPPED DENSITY

Tapped density of the powder is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time. Tapped density was measured by introducing the known quantity of the powder into a graduated cylinder and carefully leveling off the powder without compacting it. The graduated cylinder was mechanically tapped by placing on the bulk density apparatus. The volume was measured by tapping the powder blend for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. The tapped density was calculated by using the formula,

$$\rho_t = M/ V_t$$

Where,

ρ_t = Tapped density,

M = Weight of the sample in gm,

V_t = Tapped volume of the powder blend in cm^3.

4.5.4.1.4. COMPRESSIBILITY INDEX[96]

The compressibility index is measure of the propensity of a powder to consolidate. As such, it is a measure of the relative importance of inter-particulate interactios. In a free-flowing powder, such interactions are generally less significant and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions bridging between particles often results in lower bulk density and a greater difference between the bulk and tapped densities. These differences in particle interactions are reflected in the compressibility index. Compressibility index was calculated from the bulk and tapped density using the following formula,

$$\text{Compressibility index}(\%) = [\frac{TD - BD}{TD}] \times 100$$

Where,

TD = Tapped density

BD = Bulk density

4.5.4.1.5. HAUSNER'S RATIO

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Hausner's ratio was calculated from the bulk and tapped density using the following formula,

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

Table: 10 Scale of Flowability

Flow Character	Compressibility Index (%)	Hausner's Ratio
Excellent	<10	1.00 – 1.11
Good	11 – 15	1.12 – 1.18
Fair	16 – 20	1.19 – 1.25
Passable	21 – 25	1.26 – 1.34
Poor	26 – 31	1.35 – 1.45
Very poor	32 – 37	1.46 – 1.59
Extremely poor	>38	>1.60

4.5.5. FORMULATION OF ONDANSETRON HYDROCHLORIDE ORALLY DISINTEGRATING TABLETS BY DIRECT COMPRESSION METHOD

Orally disintegrating tablets of Ondansetron hydrochloride were prepared by direct compression method as per the composition shown in Table: 11. Seven formulations (F-I to F-VII) were prepared by direct compression method.

DIRECT COMPRESSION METHOD

Sieving

The active ingredient was passed through the sieve # 40. The other ingredients given in the formulation table were passed separately through the same sieve.

Dry mixing

All the materials (including the active ingredient) were taken in poly bag and mixed for 10 minutes.

Lubrication

The magnesium stearate was passed through the sieve # 60 and mixed together with the powder mixture in a polybag for 5 minutes to get a uniform blend.

Compression

Finally, the powder mixture was compressed into tablets using rotary tablet compression machine of punch size 7.14mm to prepare tablets each weighing 140mg.

Packing

The prepared tablets were packed by using PVC-Alu Blister packing.

FORMULATION FLOWCHART OF DIRECT COMPRESSION METHOD

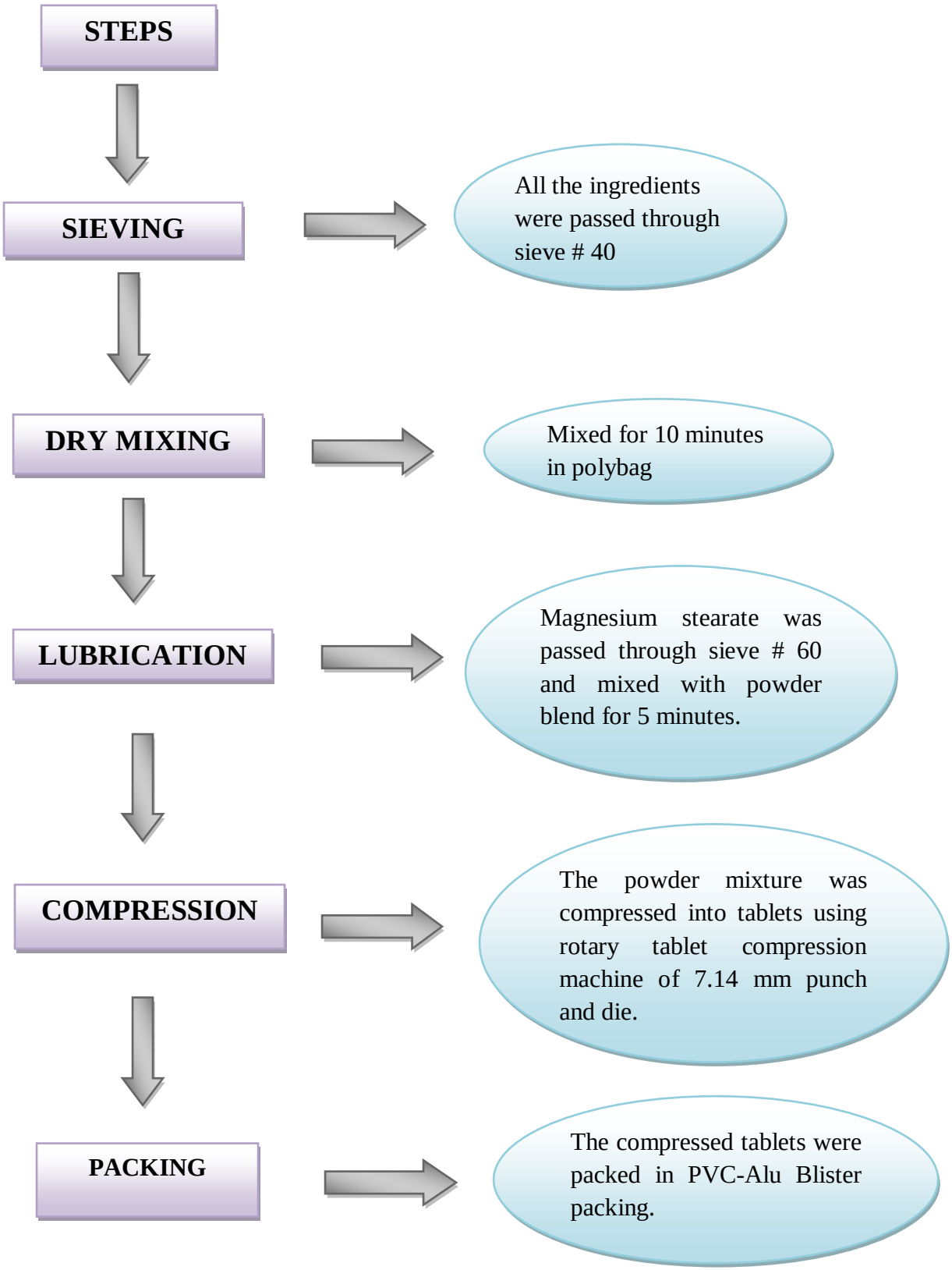


Table: 11 Composition of Ondansetron Hydrochloride Orally Disintegrating Tablets

Ingredients	Quantity per Tablet (mg)						
	Formulation Code						
	F-I	**F-II**	**F-III**	**F-IV**	**F-V**	**F-VI**	**F-VII**
Ondansetron hydrochloride	4.00	4.00	4.00	4.00	4.00	4.00	4.00
Mannitol (anhydrous)	116.80	116.80	116.80	-	-	-	70.08
Sorbitol (granular grade)	-	-	-	116.80	116.80	116.80	-
Microcrystalline cellulose (MCC-112)							46.72
Sodium starch glycolate	14.00	-	-	14.00	-	-	-
Croscarmellose sodium	-	14.00	-	-	14.00	-	-
Crospovidone	-	-	14.00	-	-	14.00	14.00
Methylparaben	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Propylparaben	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Sucralose	1.40	1.40	1.40	1.40	1.40	1.40	1.40
Sunset yellow FCF	0.70	0.70	0.70	0.70	0.70	0.70	0.70
Strawberry flavor	1.40	1.40	1.40	1.40	1.40	1.40	1.40
Magnesium stearate	0.70	0.70	0.70	0.70	0.70	0.70	0.70
Weight of each Tablets	**140**	**140**	**140**	**140**	**140**	**140**	**140**

4.5.6. POST COMPRESSION PARAMETERS

The compressed tablets were evaluated for the following parameters.

4.5.6.1. GENERAL APPEARANCE

The tablet should be free from cracks, depressions, pinholes etc. The color and polish of the tablets should be uniform on whole surface. The surface of the tablets should be smooth. The tablets were examined externally under a biconvex lens for surface cracks, depression and pinholes.

4.5.6.2. HARDNESS TEST[97]

Tablet requires a certain amount of mechanical strength to withstand the shock of handling in its manufacture, packaging, shipping and dispensing. It may be especially important to monitor the tablet hardness for sustained release drug products or other products that possess real or potential bioavailability problems or sensitive to variations in drug release profile.

The crushing strength that just causes the tablet to break is recorded by means of Monsanto hardness tester. The tablet is placed vertically in between the lower and upper plungers. The initial reading was taken immediately after placing the tablet onto the lower plunger. The upper plunger was then forced against a spring by turning a threaded bolt until the tablet gets fractured. As the spring was compressed, a point moves along a gauge in the barrel to indicate pressure. The position of the pointer at the time of tablet fracture was noted and the difference between the initial and the final readings was noted as hardness of the tablet. The value was expressed in Kg/cm^2.

4.5.6.3. THICKNESS

The thickness of the individual tablets was measured by using Vernier caliper and average thickness is determined. The thickness was denoted in millimeter.

4.5.6.4. WEIGHT VARIATION TEST[98]

Twenty tablets were selected at random and its individual weight was noted and from that, the mean weight of the tablets was calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in table: 12 and none should deviate by more than twice that percentage.

Table: 12 Weight Variation of Tablets and Percentage Deviation

Average Weight of Tablets(mg) in I.P	Percentage Deviation (%)
130 or less	±10
130 – 324	±7.5
More than 324	±5

4.5.6.5. FRIABILITY[99]

Friability is the measure of tablet's ability to withstand both shock and abrasion without crumbling during manufacturing, packing, shipping and consumer use. Tablets that tend to powder, chip and fragment when handled lack elegance and hence consumer acceptance.

The weight of 10 tablets was noted and placed in Roche friabilator. The device subjects the tablets to the combined effect of shock and abrasion by utilizing a plastic chamber which revolves at 25 rpm, rolling the tablets a distance of 6 inches with the revolution. The tablets were removed after 100 revolutions, dedusted and reweighed. Tablets that loose less than 0.5 to 1 percent in weight are generally acceptable. The percentage friability of the tablets were calculated by the formula,

$$\text{Percentage Friability} = \frac{Initial\ Weight - Final\ Weight}{Initial\ Weight} \text{ x } 100$$

4.5.6.6. DISINTEGRATION TEST[100]

Disintegration test was carried out at $37^0C \pm 2^0C$ in 900 ml of distilled water. The disintegration time of tablets from each formulations were determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus containing distilled water. One disk was added to each tube. The time taken in seconds for complete disintegration of the tablets with no palpable mass remaining in the apparatus was measured.

4.5.6.7. WETTING TIME AND WATER ABSORPTION RATIO[101]

A piece of tissue paper folded twice was placed in a small petri dish of 6.5cm in diameter containing 6ml of water. A preweighed tablet was placed on the surface of tissue paper and allowed to completely wet. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. The wetted tablet was then weighed. Water absorption ratio (R) was determined using the following equation,

$$R = \frac{Wa - Wb}{Wb} X\ 100$$

Where,

Wb - Weight of tablet before wetting.

Wa - Weight of tablet after wetting.

4.5.6.8. *IN VITRO* DISPERSION TIME[102]

Tablet was placed in a small petri dish containing 10ml of water and time required for the complete dispersion of tablet was determined.

4.5.6.9. FINENESS OF DISPERSION[103]

The fineness of dispersion test was done by using two tablets in 100ml of water and stir gently until completely dispersed. The smooth dispersion obtained was passed through a sieve screen with a nominal mesh aperture of 710mm (Sieve #22).

4.5.6.10. ASSAY OF ONDANSETRON HCl BY HPLC METHOD[71]

Chromatographic Conditions:

Column	:	LICHROSPHER , CN, 250 × 4.6mm.
Mobile phase	:	52 ml buffer solution, 48 ml Acetonitrile (ACN).
Buffer	:	0.272% w/v solution of monobasic potassium phosphate. Adjust to pH 5.4 with 1M sodium hydroxide.
Flow rate	:	1.5 ml/minute.
Injection volume	:	10 µl.
Wavelength	:	248 nm.
Temperature	:	30°C.

Preparation of Mobile Phase

Buffer and ACN were mixed in the ratio of 52:48. The pH of the mobile phase was adjusted to 5.4.

Preparation of Standard Solution

0.004% w/v solution of Ondansetron reference standard in 0.1M hydrochloric acid.

Preparation of Sample Solution

20 tablets were weighed and powdered. The powder equivalent to 40mg of Ondansetron was dissolved in 100 ml of 0.1M hydrochloric acid. 1.0 ml of this solution was diluted to 10 ml with 0.01 M hydrochloric acid.

Sample Injection Procedure

10 µl of filtered sample solution and standard solution were separately injected into HPLC system. The chromatogram was recorded and responses were measured for major peaks.

The content of Ondansetron in the powder mixture was calculated by using the following equation,

$$\text{Content of Ondansetron} = \frac{\text{Sample area}}{\text{Standard area}} \times \frac{\text{Standard weight}}{\text{Sample weight}} \times \frac{P}{100} \times \text{Avg.Wt}$$

Where,

Avg. Wt - Average weight in mg

P - Purity of Ondansetron hydrochloride.

4.5.6.11. *IN VITRO* DISSOLUTION STUDIES[71]

Dissolution Parameters

Apparatus	:	USP Dissolution apparatus, type I (Basket)
Medium	:	500 ml of 0.1 M Hydrochloric acid
RPM	:	50
Temperature	:	37°C ± 0.5°C
Sampling interval	:	2, 4, 6, 8, 10 minutes
Sample withdrawn	:	5ml
Wavelength	:	310nm
Instrument	:	UV spectroscopy

Preparation of 0.1 M Hydrochloric Acid

Place 8.5 ml of concentrated hydrochloric acid into the 1000 ml volumetric flask and the volume were made up with de-mineralized water.

Procedure

The *in vitro* dissolution studies of Ondansetron HCl orally disintegrating tablets were performed using USP dissolution apparatus type 1(basket). The volume of dissolution medium (0.1M HCl) used was 500 ml and the temperature was maintained at 37°C±0.5°C. The speed of the basket was set at 50rpm. One tablet was placed in each jar of dissolution apparatus. 5ml of sample from each jar was withdrawn at every 2 minutes interval upto 10 minutes and same volume of 0.1M HCl was replaced to each dissolution jar, so that volume of dissolution medium was maintained to 500ml. Then the sample was filtered and diluted with 0.1M HCl and the amount of Ondansetron HCl released from ODT^S was determined spectrophotometrically at 310 nm using 0.1M HCl as blank.

4.5.6.12. STABILITY STUDIES[104]

Stability of a formulation can be defined as the time from date of manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

Formulation and the development of a pharmaceutical product is not complete without proper stability analysis. It is carried out to assess the physical and chemical stability and safety use of the product. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf lives.

4.5.6.12.1 ACCELERATED STABILITY STUDIES

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of accelerated stability studies are adopted by accelerating the parameters such as temperature, humidity and light.

The International Council for Harmonization (ICH) guidelines titled "Stability testing of new drug substances and product" (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and United States of America. ICH specifies the length of study and storage conditions.

- Long –term testing: $25 \pm 2°C/60\% \pm 5\%$ RH for 12 months.
- Accelerated testing: $40 \pm 2°C/75\% \pm 5\%$ RH for 6 months.

Procedure

Stability studies were carried out optimized formulation at $25 \pm 2°C/60 \pm 5\%$ RH and $40 \pm 2°C/75\% \pm 5\%$ RH for (F-VII) for 3 months. The selected clear ALU-ALU packed formulations were stored at $25 \pm 2°C/60\% \pm 5\%$ RH and $40 \pm 2°C/75\% \pm 5\%$ RH for 3 months and their physical appearance, average weight, thickness, hardness, friability, disintegration test, *in vitro* dispersion time, fineness of dispersion, assay and *in vitro* drug release were evaluated at specified intervals of time(every month).

CHAPTER-5

Results and Discussion

CHAPTER-5

5. RESULTS AND DISCUSSION

The present study was undertaken to formulate Ondansetron hydrochloride orally disintegrating tablets by direct compression method using three superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate. The study was aimed to prevent inherent drawbacks associated with conventional tablets of Ondansetron hydrochloride such as risk of choking, bitter taste and difficult in swallowing by formulating Ondansetron hydrochloride ODT^S. Preformulation studies were carried out before the formulation in which certain parameters were evaluated. A total of seven formulations were prepared to achieve rapid oral disintegration of Ondansetron hydrochloride (three trials by addition of mannitol anhydrous, three trials by sorbitol granular grade and one trial by both mannitol anhydrous and microcrystalline cellulose (MCC-112).

The prepared blend of seven different formulations were evaluated for precompression parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The prepared tablets were also evaluated for various post compression parameters like appearance, thickness, hardness, weight variation, friability, disintegration test, wetting time, water absorption ratio, *in vitro* dispersion time, fineness of dispersion, drug content and *in vitro* dissolution studies.

5.1 PREFORMULATION STUDIES

5.1.1. ORGANOLEPTIC PROPERTIES

The organoleptic properties of Ondansetron hydrochloride were presented in Table: 13

Table: 13 Organoleptic Properties of Ondansetron HCl (API)

Tests	Specification	Observation
Color	White	White
Odor	Odorless	Odorless
Taste	Bitter	Bitter

Discussion

The organoleptic properties like color, odor and taste of the API were evaluated. The color of Ondansetron HCl was found to be white or almost white powder, no characteristic odor was observed in the study and the taste was found to be bitter. Ondansetron hydrochloride showed similar color, taste and odor as per IP specification.

5.1.2. SOLUBILITY TEST

The solubility profile of Ondansetron hydrochloride was presented in Table: 14.

Table: 14 Solubility Analysis of Ondansetron HCl (API)

Raw Material (API)	Solubility
Ondansetron HCl	Sparingly soluble in water
	Sparingly soluble in ethanol
	Soluble in methanol

Discussion

The solubility studies of drug (API) revealed that Ondansetron HCl was sparingly soluble in water and ethanol and soluble in methanol.

5.1.3. DRUG - EXCIPIENTS COMPATIBILITY STUDIES

Compatibility studies were performed by preparing blend of different excipients with drug and stored at $40^{O}C \pm 2^{O}C$ /75±5%RH for one month. The blends were evaluated for every 15 days for changes like caking, liquefaction, discoloration and odor formation. The results were given in table: 15.

Table: 15 Drug- Excipients Compatibility Study

S. No.	Composition	Initial Period	After 15 Days	After 30 Days
1	Ondansetron HCl	White to off white powder with no characteristic odor	NCC	NCC
2	Ondansetron HCl + Mannitol anhydrous		NCC	NCC
3	Ondansetron HCl + Sorbitol granular grade		NCC	NCC
4	Ondansetron HCl + Microcrystalline cellulose (MCC-112)		NCC	NCC
5	Ondansetron HCl + Sodium starch glycolate		NCC	NCC
6	Ondansetron HCl + Croscarmellose sodium		NCC	NCC
7	Ondansetron HCl + Crospovidone		NCC	NCC
8	Ondansetron HCl + Methylparaben		NCC	NCC
9	Ondansetron HCl + Propylparaben		NCC	NCC
10	Ondansetron HCl + Sucralose		NCC	NCC
11	Ondansetron HCl + Magnesium stearate		NCC	NCC
12	Ondansetron HCl + Sunset yellow FCF	Yellow color powder	NCC	NCC
13	Ondansetron HCl + Strawberry flavor	White to off white powder with strawberry odor	NCC	NCC

NCC: No Characteristic Change

Discussion

From the above drug excipients compatibility study, it was observed that there was no characteristic change found between the drug and excipients. Thus it was concluded that the excipients selected for the formulation were compatible with Ondansetron hydrochloride and suitable for formulation development.

5.2 FT-IR SPECTRAL STUDIES

FT-IR studies of the pure Ondansetron, superdisintegrants and combination of drug and superdisintegrants containing highest proportion were carried out to found any interaction between drug and excipients used in the formulation. FT-IR study was performed using IR spectroscopy (SHIMADZU). The results are shown in fig: 6 to 12 and in table: 16 to 22. The comparison of FT-IR spectral data of drug with superdisintegrants was given in table: 23**.**

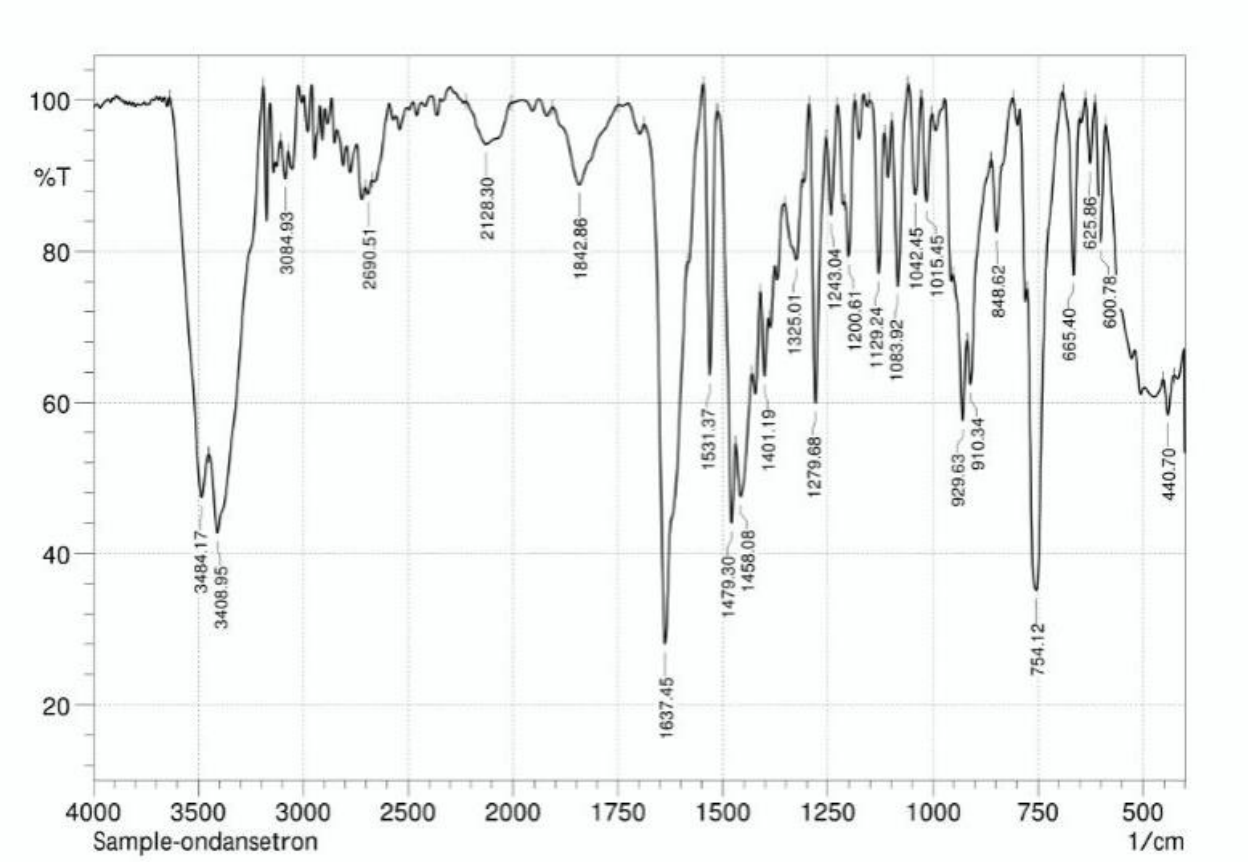


Fig: 6 FT-IR Spectrum of Pure Ondansetron Hydrochloride

Table: 16 FT-IR Spectral Data of Pure Ondansetron Hydrochloride

S.no	Wave Number(cm^{-1})	Functional Group
1	3408	Broad band of bonded OH
2	1637	C=O of aryl acids stretching
3	1458	C=N stretching
4	1420	Aromatic C=C stretching
5	1083	C-N stretching
6	754	CH_3 angular

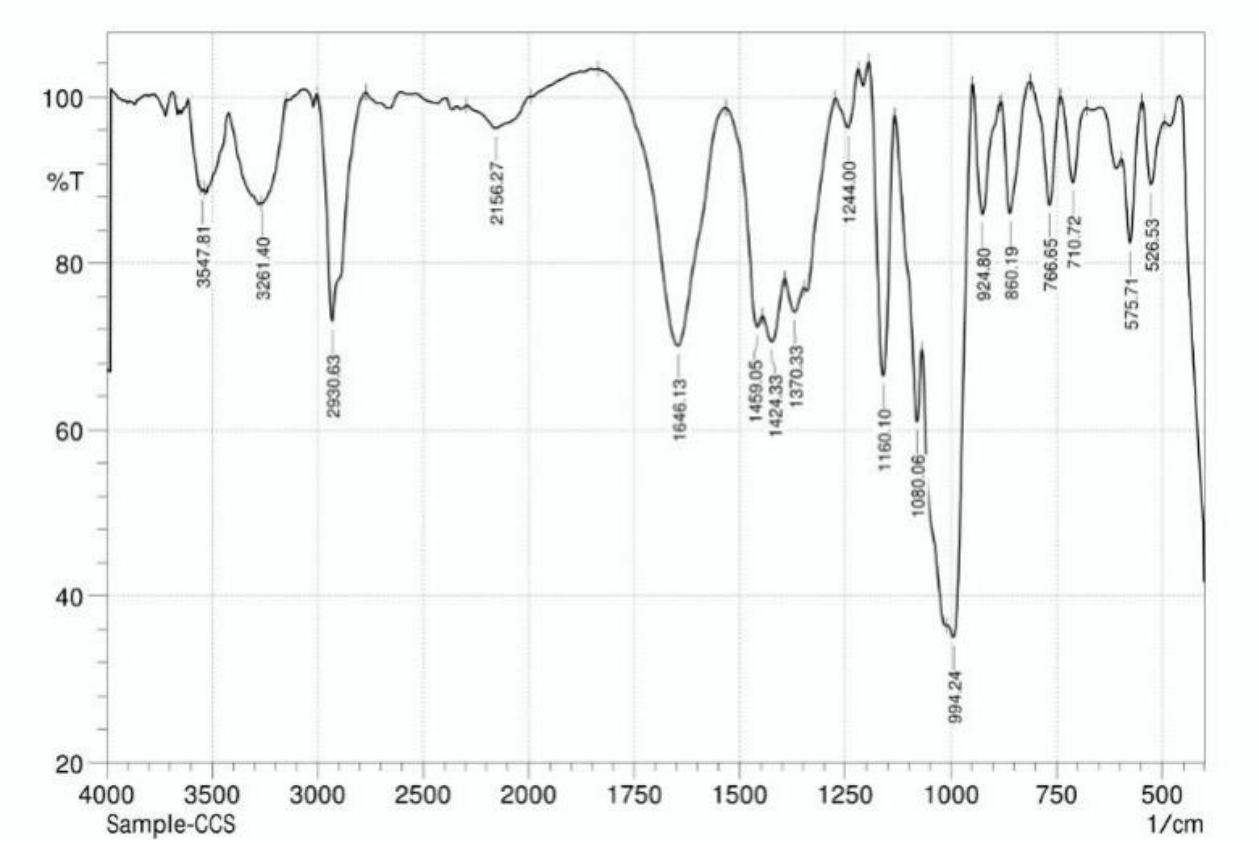


Fig: 7 FT-IR Spectrum of Croscarmellose sodium

Table: 17 FT-IR Spectral Data of Croscarmellose sodium

S.no	Wave Number(cm^{-1})	Functional Group
1	3547	OH stretching
2	2930	Aliphatic C-H stretching
3	1646	C=O stretching
4	1080	C-O stretching
5	994	C-O-C group
6	710	CH_2 Alkane

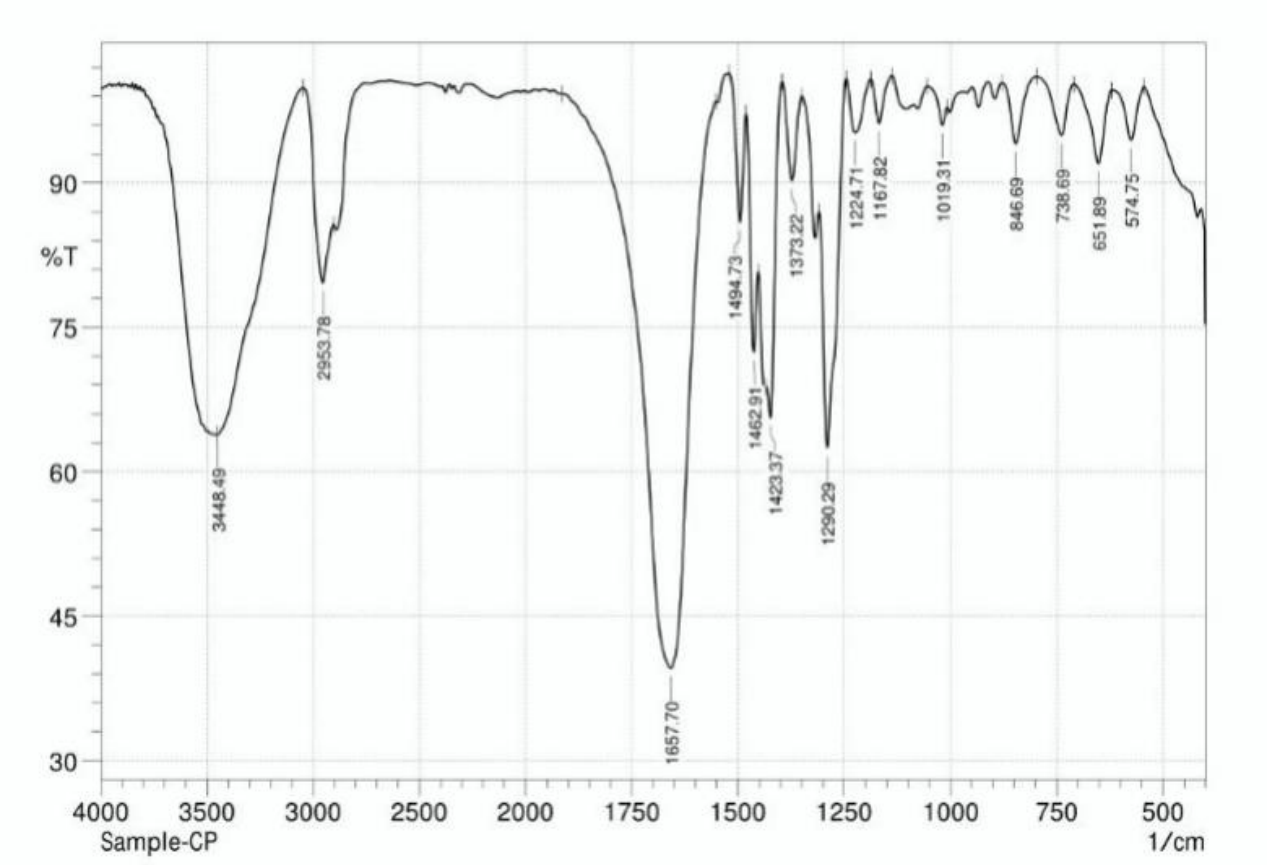


Fig: 8 FT-IR Spectrum of Crospovidone

Table: 18 FT-IR Spectral Data of Crospovidone

S.no	Wave Number(cm^{-1})	Functional Group
1	3448	OH stretching
2	2953	Aliphatic C-H
3	1657	C=O stretching
4	1290	C-N stretching
5	738	C-H methane
6	651	CH_2 group

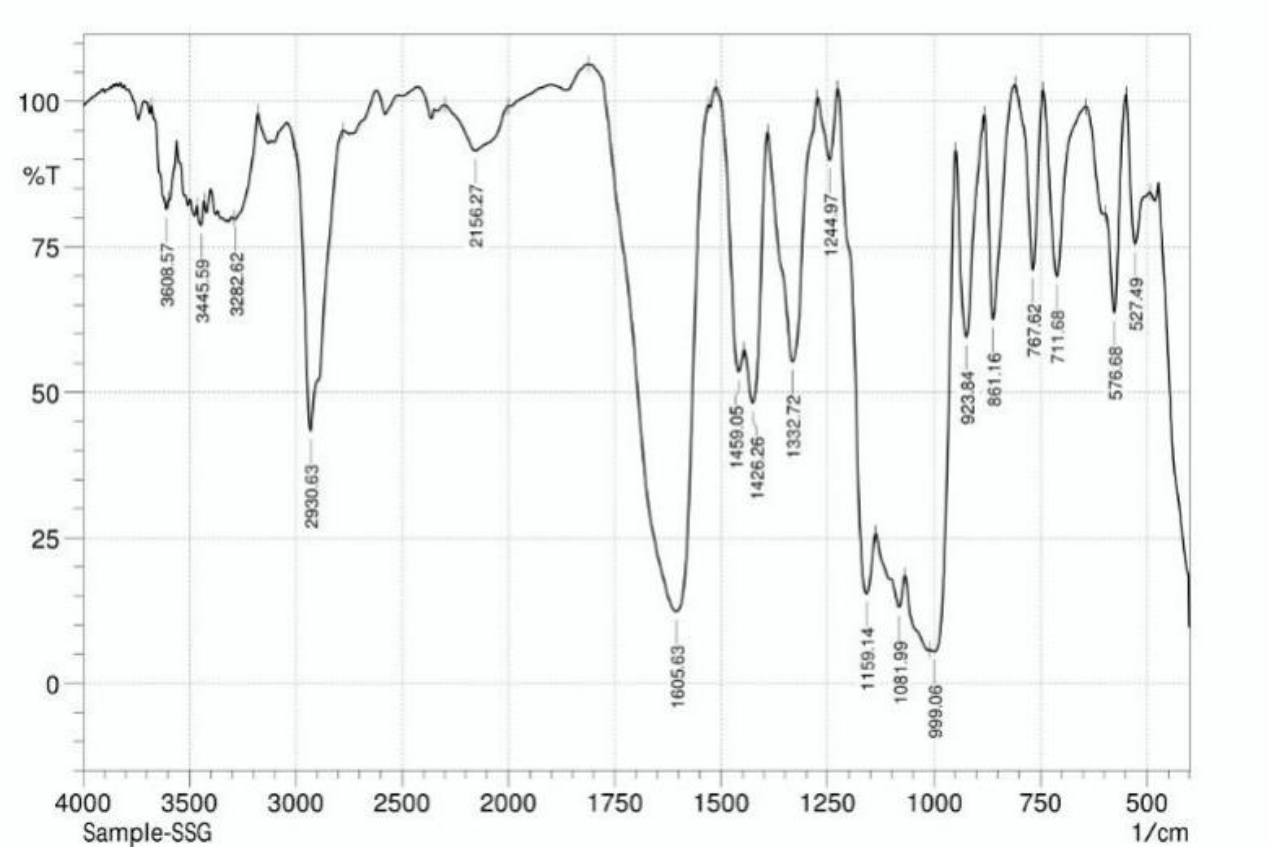


Fig: 9 FT-IR Spectrum of Sodium starch glycolate

Table: 19 FT-IR Spectral Data of Sodium starch glycolate

S.no	Wave Number(cm^{-1})	Functional Group
1	3282	OH bending
2	1605	C=O stretching
3	1159	C-O stretching
4	767	C-C stretching

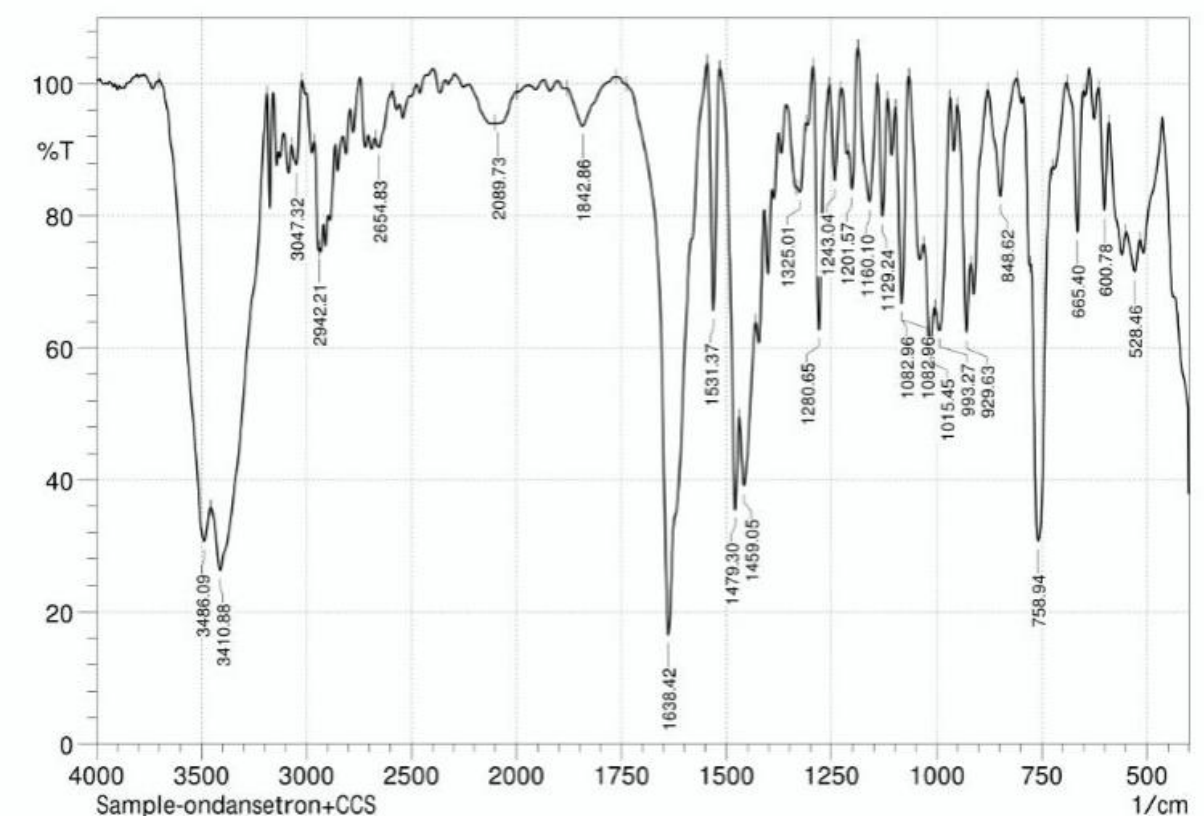


Fig: 10 FT-IR Spectrum of Ondansetron Hydrochloride + Croscarmellose sodium

Table: 20 FT-IR Spectral Data of Ondansetron Hydrochloride + Croscarmellose sodium

S.no	Wave Number(cm^{-1})	Functional Group
1	3486	OH stretching
2	3047	Aromatic C-H
3	2942	Aliphatic C-H
4	1638	C=O stretching
5	1531	Aromatic C=C
6	1082	C-N bending
7	993	C-O stretching
8	758	CH_3 group

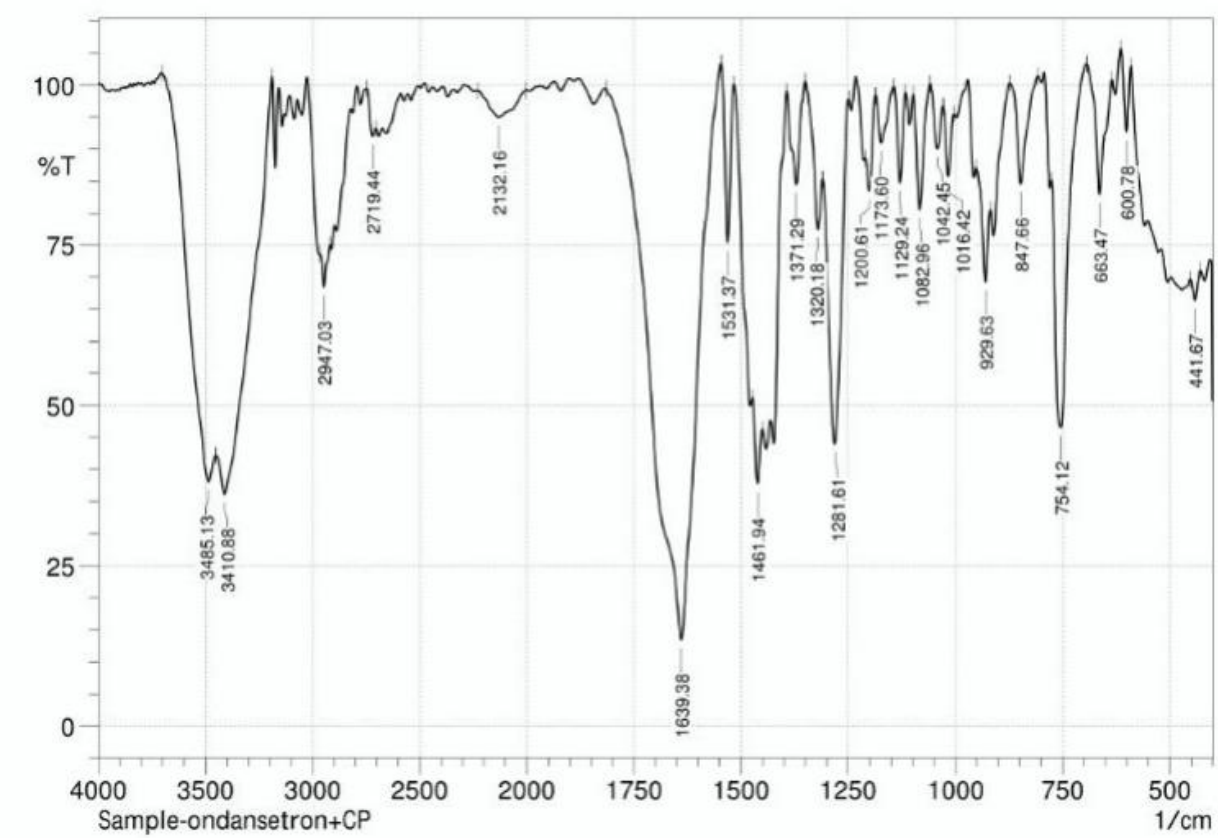


Fig: 11 FT-IR Spectrum of Ondansetron Hydrochloride + Crospovidone

Table: 21 FT-IR Spectral Data of Ondansetron Hydrochloride + Crospovidone

S.no	Wave Number(cm^{-1})	Functional Group
1	3642	Aromatic C-H
2	3485	OH bending
3	2947	Aliphatic C-H
4	1639	C=O stretching
5	1531	C=C stretching
6	1461	C=N stretching
7	1082	C-N stretching
8	1042	C-O stretching

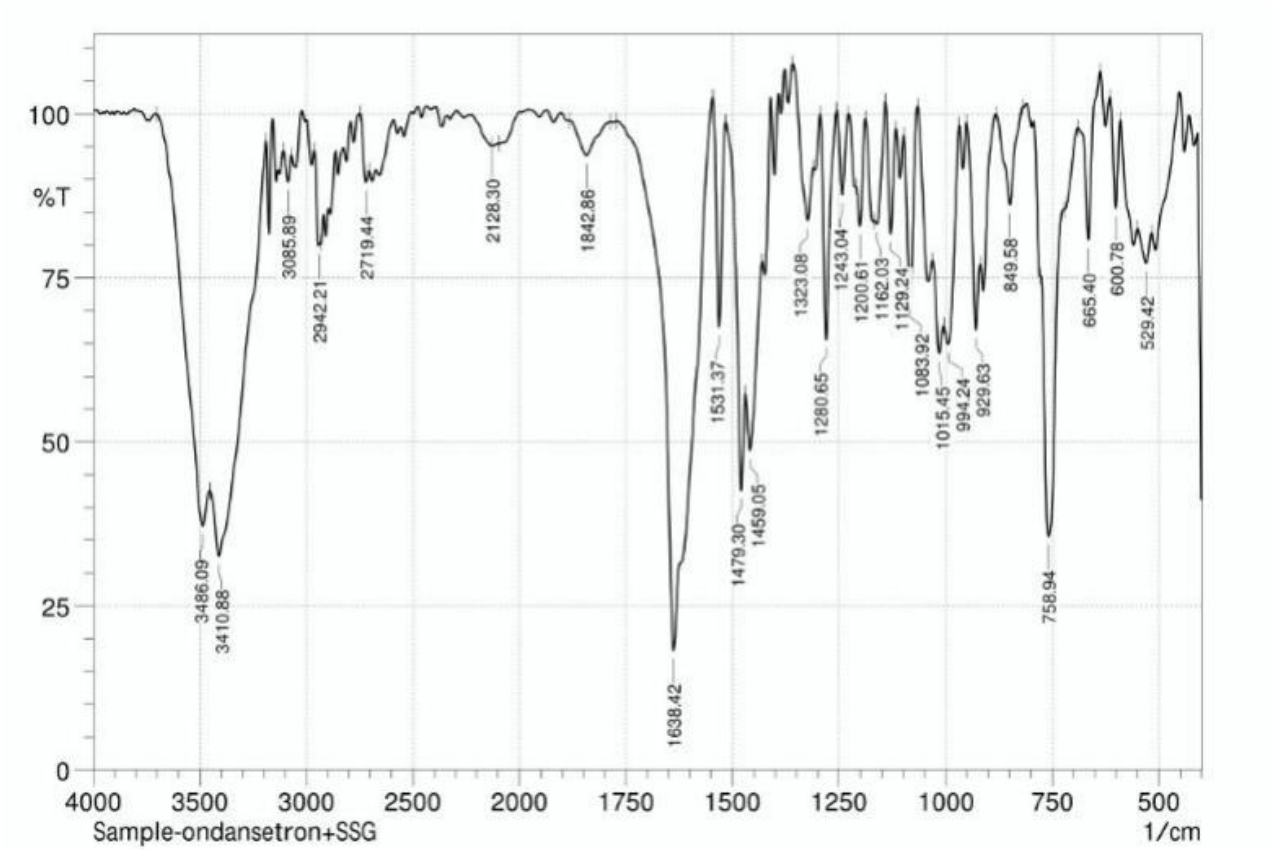


Fig: 12 FT-IR Spectrum of Ondansetron Hydrochloride + Sodium starch glycolate

Table: 22 FT-IR Spectral Data of Ondansetron Hydrochloride + Sodium starch glycolate

S.no	Wave Number(cm^{-1})	Functional Group
1	3486	OH bending
2	3085	CH aromatic
3	2942	Aliphatic CH
4	1638	C=O stretching
5	1531	C=C stretching
6	1459	CH_2 group
7	1015	C-O stretching
8	758	Aliphatic CH_3

Table: 23 Comparative FT-IR Spectral Data of Drug and Superdisintegrants

Compounds	Functional Groups				
	OH (cm^{-1})	**C=O (cm^{-1})**	**C=C (cm^{-1})**	**C-O (cm^{-1})**	**Aliphatic CH_3 (cm^{-1})**
Drug (Ondansetron Hydrochloride)	3408	1637	1420	1040	754
Drug + CCS	3486	1638	1531	993	758
Drug + CP	3485	1639	1531	1042	758
Drug + SSG	3486	1638	1531	1015	758

Discussion

FT-IR spectral studies indicated that the drug is compatible with all the excipients. The FT-IR spectrum of physical mixture showed all the characteristic peaks of Ondansetron hydrochloride, thus conforming that no interaction of drug occurred with the components of the formulation.

5.3 EVALUATION OF PRECOMPRESSION PARAMETERS

5.3.1. MICROMERITIC PROPERTIES

The powder blends were evaluated for the following parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results were given below in Table: 24

Table: 24 Precompression Parameters

Formulation Code	Angle of Repose (θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's ratio
F-I	32^o.11'	0.562	0.690	18.55	1.22
F-II	29^o.09'	0.640	0.745	14.09	1.16
F-III	27^o.06'	0.305	0.351	13.11	1.15
F-IV	29^o.98'	0.317	0.367	13.63	1.15
F-V	26^o.23'	0.310	0.360	13.89	1.16
F-VI	25^o.09'	0.318	0.378	15.87	1.18
F-VII	22^o.98'	0.311	0.368	15.21	1.18

Discussion

The angle of repose of formulation F-I was found to be 32^o.11' which indicates good flow property. Angle of repose of all the other formulations were found to be between 22^o.98' to 29^o.98' which indicates excellent flow property.

The bulk density was found to be between 0.305 to 0.640 g/cm^3, the tapped density was found to be between 0.351 to 0.745 g/cm^3, the compressibility index was found in the range of 13.11 to 18.55% and the Hausner's ratio lies between 1.15 to 1.22.

The above results in terms of micromeritic properties revealed that the flow property of formulation F-I was fair and other formulations were good.

5.4. EVALUATION OF ONDANSETRON HYDROCHLORIDE ODT[S]

5.4.1. POST COMPRESSION PARAMETERS

5.4.1.1. GENERAL APPEARANCE

The general appearance of all formulations (F-I to F-VII) were examined and found as follows,

Color - Orange

Shape - Round

Surface – Smooth

Cracks, depressions, pinholes - Absent

The prepared tablets were evaluated for various post compression parameters. The results are presented in Table: 25 and 26.

Table: 25 Post Compression Parameters

Formulation Code	Thickness (mm)	Hardness (kg /cm^2)	Weight Variation (mg)	Friability (%)
F-I	3.20± 0.055	4.50± 0.32	142±1.25	0.24
F-II	3.30± 0.010	4.50± 0.22	140±0.65	0.42
F-III	3.20± 0.017	3.00± 0.27	140±0.46	0.50
F-IV	3.40 ± 0.016	4.50± 0.21	143±0.89	0.46
F-V	3.40 ± 0.020	4.50± 0.49	140±0.45	0.32
F-VI	3.20± 0.062	3.50± 0.29	142±0.96	0.20
F-VII	3.30± 0.018	3.00± 0.24	141±1.45	0.15
Marketed sample	2.90± 0.055	3.50± 0.32	140±0.89	0.26

All the values are expressed as mean± SD, n=3

Discussion

The thickness of the tablets was measured and were found in the range between 3.20 ± 0.017 mm to 3.40 ±0.020mm. All the formulations possessed uniform thickness.

The hardness of the tablets was measured and the values were found in the range between 3.00± 0.27 to 4.50± 0.49 kg/cm^2. The prepared tablets possessed good mechanical strength with sufficient hardness.

All formulations of Ondansetron hydrochloride orally disintegrating tablets passed the weight variation test since the values are within the acceptable variation limit of the tablet.

Similarly percentage friability values of the prepared Ondansetron hydrochloride orally disintegrating tablets showed less than 1% weight loss that is highly within the acceptable limit. Hence all the tablets passed the friability test.

Table: 26 Evaluation of Ondansetron Hydrochloride ODT^{S}

Formulation Code	Disintegration Test (Sec)	Wetting Time (Sec)	Water Absorption Ratio	*In vitro* Dispersion Time (Sec)	Fineness of Dispersion
F-I	28±0.23	102±1.35	80.22±0.52	49±0.14	Passed
F-II	24±0.12	90±1.19	85.36±0.58	38±0.12	Passed
F-III	15±0.10	48±2.28	92.17±0.41	27±0.21	Passed
F-IV	24±0.45	88±0.71	79.25±0.17	39±0.14	Passed
F-V	23±0.58	81±0.10	87.12± 0.14	35±0.43	Passed
F-VI	20±0.35	56±0.21	86.98±0.12	28±0.66	Passed
F-VII	12±0.56	45±0.28	91.24±0.43	24±0.35	Passed
Marketed sample	17±0.32	54±0.45	94.31±0.21	27±0.26	Passed

All the values are expressed as mean± SD, n=3

Discussion

Disintegration time of Ondansetron hydrochloride orally disintegrating tablets ranges between 12 to 28 seconds. The acceptable disintegration time limit as per I.P is NMT 30seconds. Formulation F-VII showed least disintegration time (12 sec) compared with all other formulations.

Wetting time of Ondansetron hydrochloride orally disintegrating tablets were found to be in the range between 45 and 102 seconds. Formulation F-VII prepared by using crospovidone as superdisintegrant showed least wetting time (45 sec).

Water absorption ratio of Ondansetron hydrochloride orally disintegrating tablets were found between 79.25 to 92.31.

In vitro dispersion time of the Ondansetron hydrochloride orally disintegrating tablets were found between 24 to 49 seconds. Formulation F-VII showed rapid dispersion (24 sec) compared with all other formulations.

In fineness of dispersion test, the dispersion of all the seven formulations passed through sieve #22 and passed the test.

From the above results, it was concluded that the formulation F-VII showed better tableting properties compared to the other formulations and marketed formulation and was selected as the best formulation.

The *in vitro* dispersion time of the best formulation (F-VII) at various time intervals (0, 12, 18, 24 seconds) were shown in Fig: 13.

***In Vitro* Dispersion Time of Formulation F-VII at Various Time Intervals**

At 0 seconds

At 12 seconds

At 18 seconds

At 24 seconds

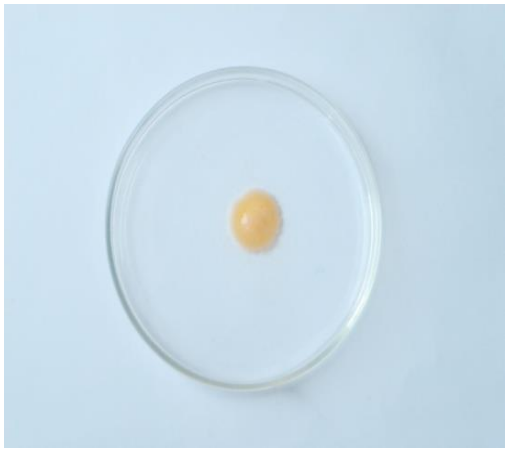
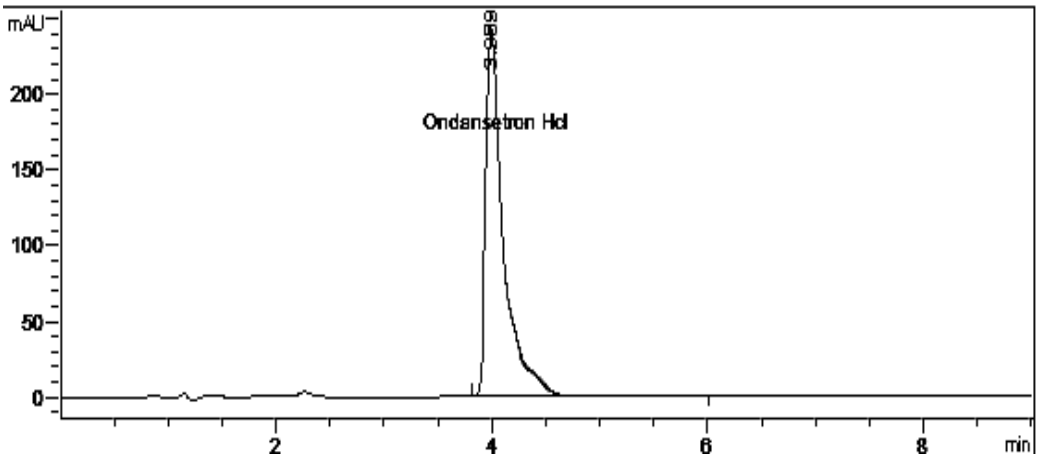


Fig: 13 *In Vitro* Dispersion of Ondansetron Hydrochloride Orally Disintegrating Tablets

5.4.2. ASSAY OF ONDANSETRON HCl BY HPLC METHOD

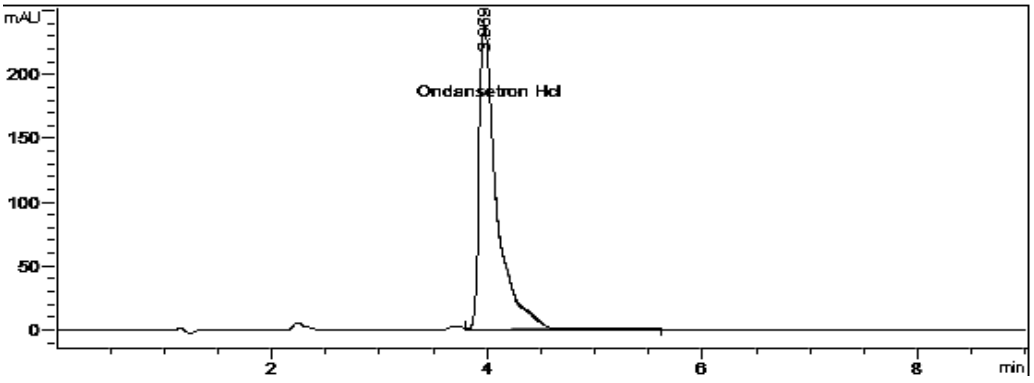
The assay was carried out by HPLC method as per the procedure given in methodology part. The HPLC chromatogram of Ondansetron hydrochloride standard and sample formulations were shown in fig no: 14 to 21 and table: 27.



S. No.	Drug	RT*	Area	Plate count	Symmetry
1	Ondansetron HCl	3.994	2825201	3959	0.88

***RT-Retention Time**

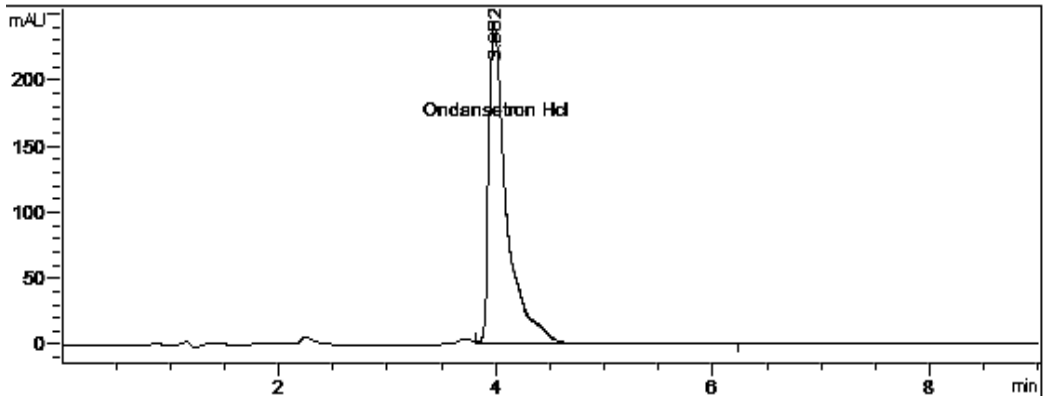
Fig: 14 HPLC Chromatogram of Ondansetron HCl (Standard)



S. No.	Name	RT*	Area	Plate count	Symmetry
1	Formulation F-I	3.969	2818015	3924	0.83

***RT-Retention Time**

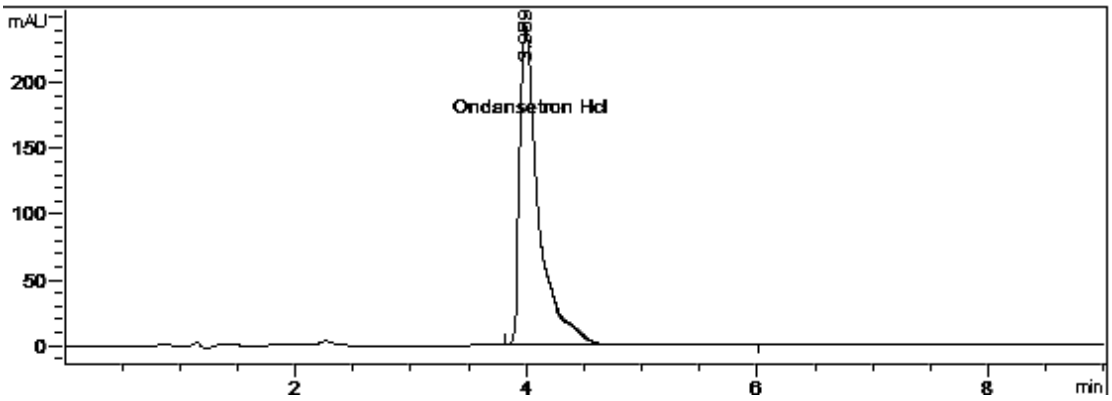
Fig: 15 HPLC Chromatogram of Formulation F-I



S.No.	Drug	RT*	Area	Plate count	Symmetry
1	Formulation F-II	3.982	2832750	3943	0.83

***RT-Retention Time**

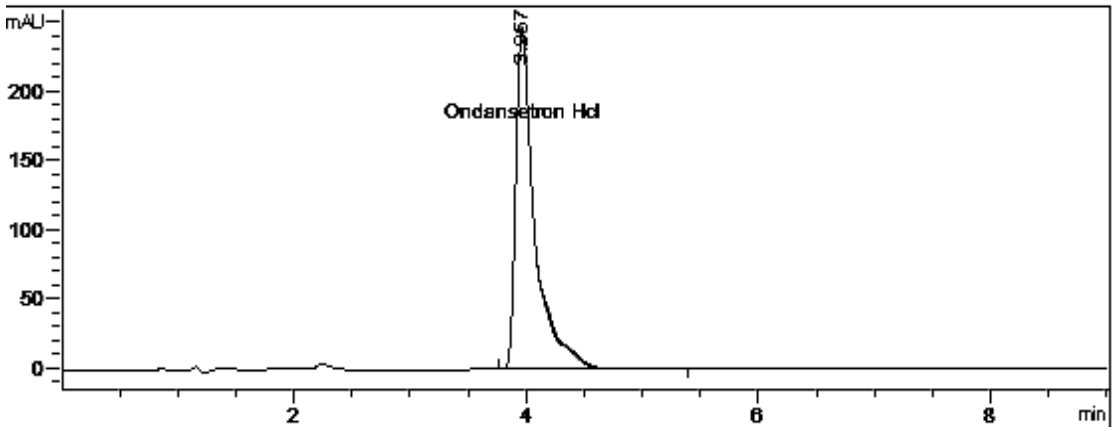
Fig: 16 HPLC Chromatogram of Formulation F-II



S.No.	Drug	RT*	Area	Plate count	Symmetry
1	Formulation F-III	3.989	2824401	3999	0.83

***RT-Retention Time**

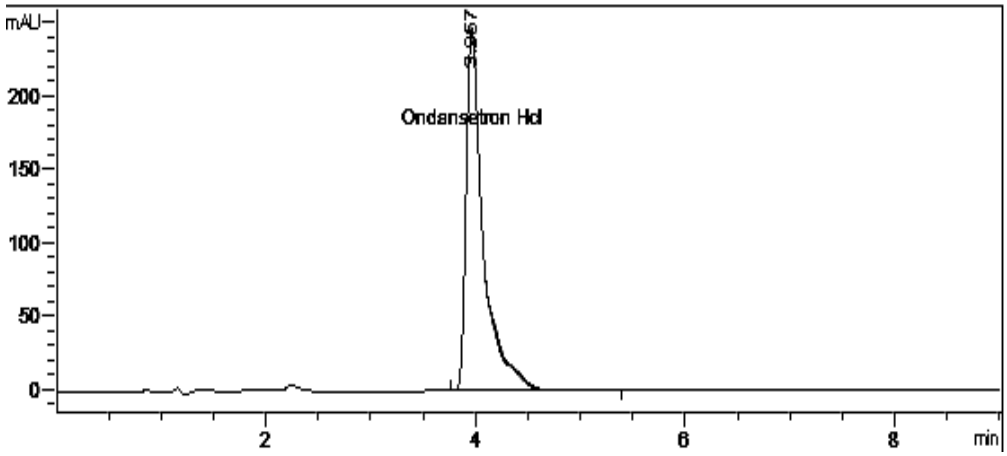
Fig: 17 HPLC Chromatogram of Formulation F-III



S.No.	Drug	RT*	Area	Plate count	Symmetry
1	Formulation F-IV	3.994	294208	4014	0.83

***RT-Retention Time**

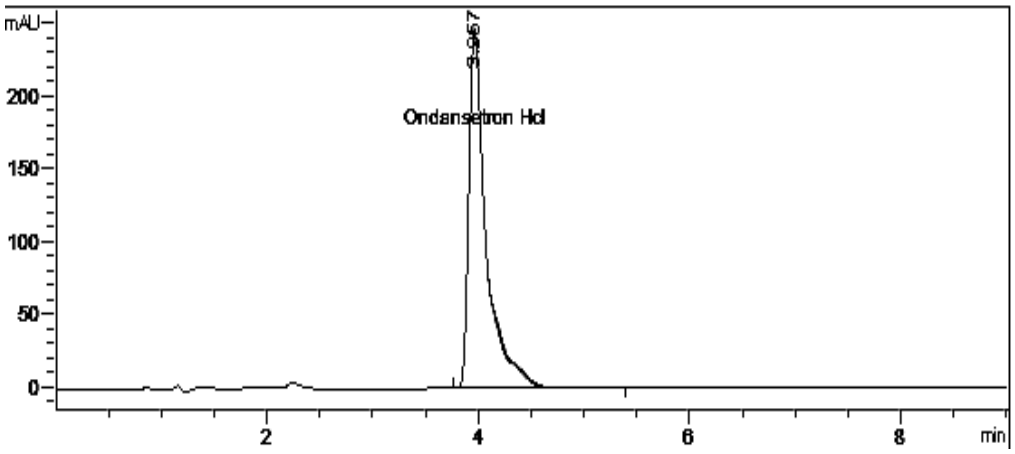
Fig: 18 HPLC Chromatogram of Formulation F-IV



S.No.	Drug	RT*	Area	Plate count	Symmetry
1	Formulation F-V	3.957	2833511	4364	0.82

***RT-Retention Time**

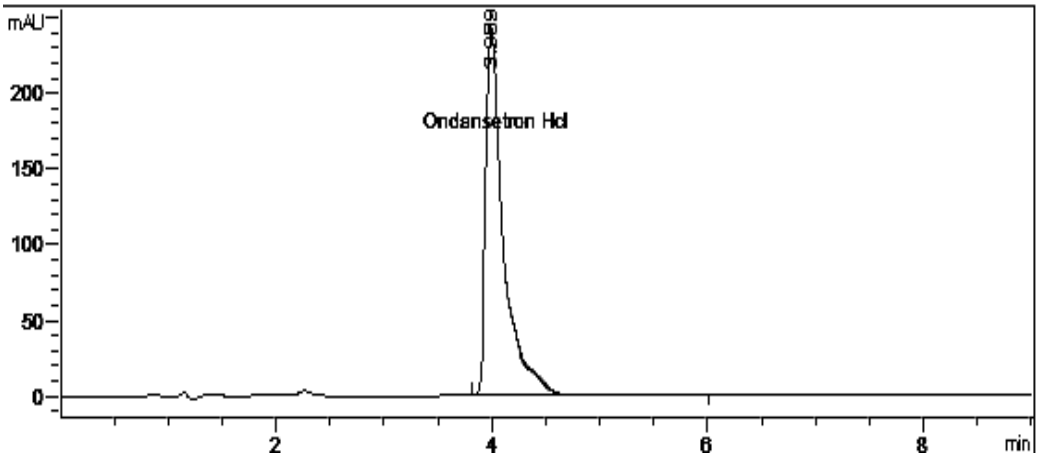
Fig: 19 HPLC Chromatogram of Formulation F-V



S.No.	Drug	RT*	Area	Plate count	Symmetry
1	Formulation F-VI	3.957	2818431	4509	0.82

***RT-Retention Time**

Fig: 20 HPLC Chromatogram of Formulation F-VI



S.No.	Drug	RT*	Area	Plate count	Symmetry
1	Formulation F-VII	3.989	2824401	3999	0.83

***RT-Retention Time**

Fig: 21 HPLC Chromatogram of Formulation F-VII

Table: 27 Assay of Ondansetron Hydrochloride Orally Disintegrating Tablets

Formulation Code	Limit (%)	Assay (%)
F-I	90 to 110%	99.50
F-II		98.85
F-III		99.75
F-IV		99.52
F-V		99.55
F-VI		98.82
F-VII		99.87
Marketed sample		98.69

Discussion

The assay of Ondansetron hydrochloride orally disintegrating tablets were found in the range between 98.82 to 99.87 %. The acceptable limit of Ondansetron content as per I.P is 90 to 110%. The results revealed that the assay of Ondansetron hydrochloride was within the acceptable limits.

5.4.3. *IN VITRO* DISSOLUTION STUDIES

The *in vitro* drug release of Ondansetron Hydrochloride ODT^S were given in table: 28 and fig: 22

Table: 28 Comparative *In Vitro* Drug Release Studies of Ondansetron Hydrochloride ODT^S

Time (min)	Percentage Drug Release (%)						
	Formulation Code						
	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII
2	20.58± 0.48	25.85± 0.37	31.48± 0.55	18.53± 0.33	22.43± 0.31	30.10± 0.58	35.30± 1.18
4	32.23± 0.70	34.71± 0.60	42.62± 0.55	31.17± 0.28	31.54± 0.52	48.52± 0.43	54.15± 0.61
6	41.63± 0.59	49.88± 0.26	61.54± 0.20	48.67± 0.43	46.64± 00.6	59.92± 0.98	72.28± 0.24
8	65.99± 1.23	69.60± 0.68	79.56± 0.44	58.96± 0.70	62.82± 0.28	74.18± 0.67	85.61± 0.52
10	72.30± 0.16	76.07± 0.50	84.34± 0.09	70.73± 0.60	73.18± 0.07	81.62± 0.11	99.85± 0.07

All the values are expressed as mean± SD, n=3

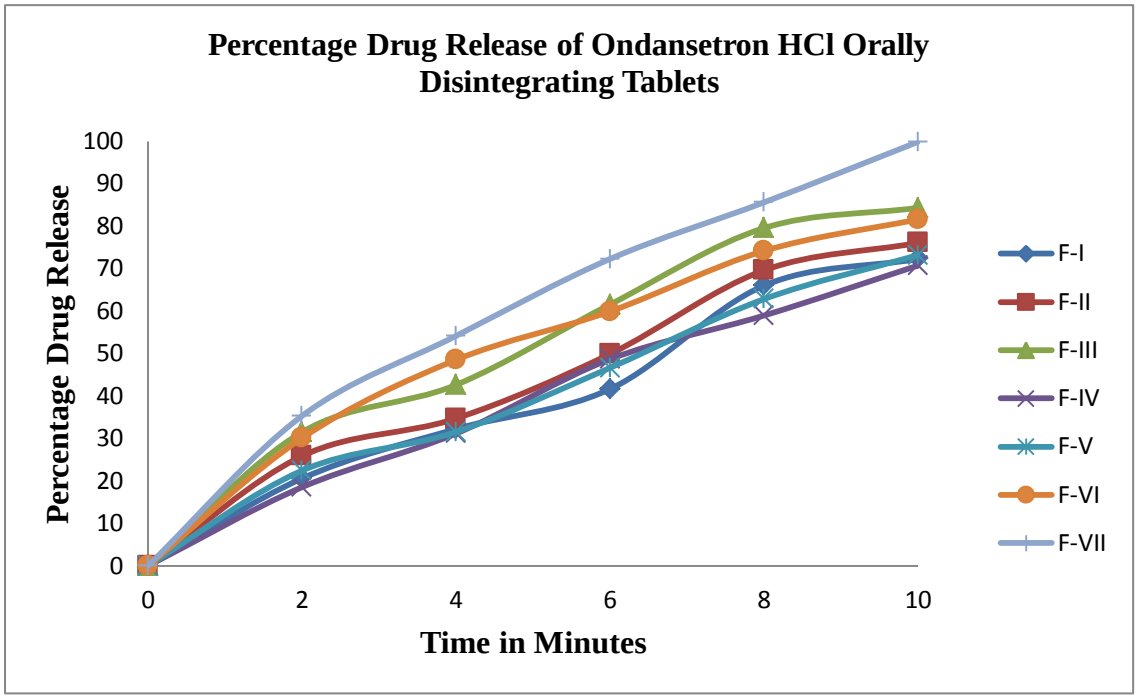


Fig: 22 Comparative *In Vitro* Drug Release Profiles of Ondansetron Hydrochloride ODT^{S}

Discussion

Ondansetron hydrochloride release was studied in 0.1M hydrochloric acid for up to 10 minutes. The formulation F-I (sodium starch glycolate), F-II (croscarmellose sodium), F-III (crospovidone) were prepared along with mannitol as diluent and the formulation F-IV (sodium starch glycolate), F-V (croscarmellose sodium), F-VI (crospovidone) were prepared along with sorbitol as diluent. Formulation F-VII (crospovidone) was prepared with microcrystalline cellulose along with mannitol as diluent.

The drug release of formulation F-I, F-II and F-III was found to be 72.30± 0.16 %, 76.07± 0.50% and 84.34± 0.09 % at 10 minutes. The drug release of formulation F-IV, F-V and F-VI was found to be 70.73± 0.60 %, 73.18± 0.07 % and 81.62± 0.11 % at 10 minutes. The drug release of formulation F-VII was found to be 99.85± 0.07 % at 10 minutes. The acceptable *in vitro* dissolution limit is NLT 80% of drug release at 10 minutes. Formulation F-III, F-VI and F- VII passed the *in vitro* dissolution studies. The higher dissolution rates were observed in formulation F-III, F-VI and F- VII prepared using crospovidone as superdisintegrant which may be due to rapid disintegration and fine dispersion of particles formed after disintegration. Formulation F-VII prepared using crospovidone as superdisintegrant showed maximum drug release. This may be due to highly porous structure of the superdisintegrant with direct compressible vehicle (microcrystalline cellulose), which

facilitates faster water uptake and hence faster disintegration, easy breakdown of particles and rapid dissolution.

The order of enhancement of the dissolution rate with various superdisintegrants was found to be CP>CCS>SSG. Formulation F-VII was observed as optimized formulation based on rapid disintegration time, wetting time, *in vitro* dispersion time and dissolution profile.

5.4.3.1. COMPARATIVE DISSOLUTION STUDY OF MARKETED FORMULATION AND OPTIMIZED FORMULATION (F-VII)

The dissolution profile of optimized formulation (F-VII) was compared with marketed Ondansetron HCl orally disintegrating tablet. The comparative drug release profiles are shown in table: 29 and fig: 23.

Table: 29 Comparative *In Vitro* Release Data of Ondansetron HCl Marketed Tablet and Optimized Formulation (F-VII)

Time (min)	Percentage Drug Release (%)	
	Formulation F-VII	Marketed Formulation
2	35.30± 1.18	20.29± 0.28
4	54.15± 0.61	32.16± 1.01
6	72.28± 0.24	54.57± 0.94
8	85.61± 0.52	70.59± 0.51
10	99.85± 0.07	82.52± 0.43

All the values are expressed as mean± SD, n=3

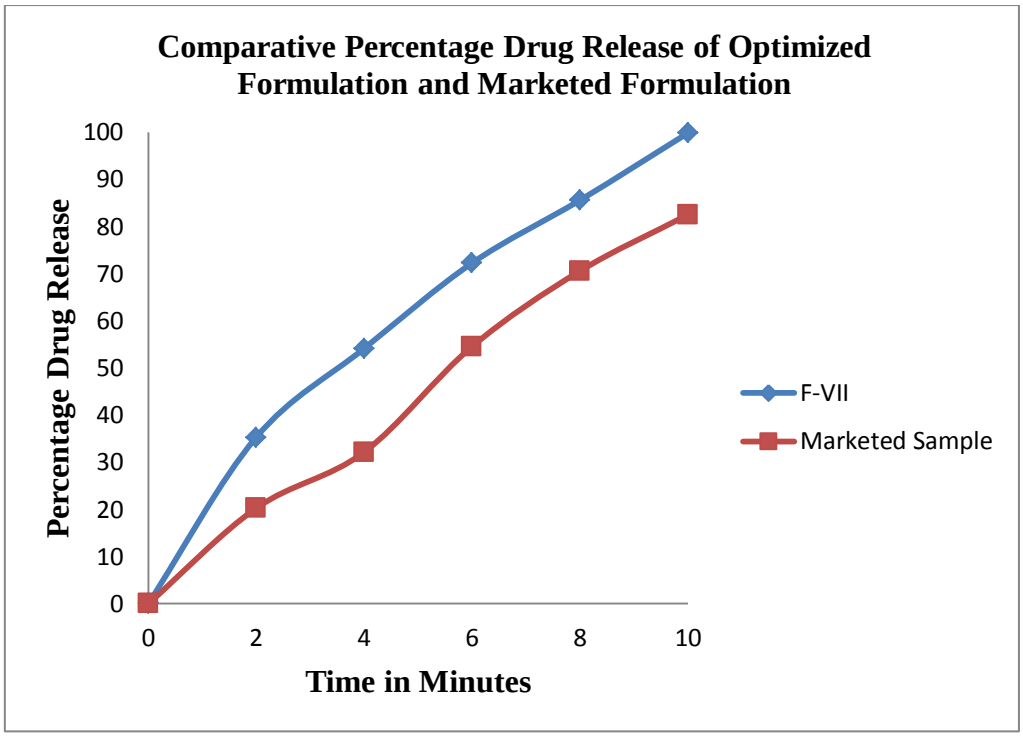


Fig: 23 Comparative *In Vitro* Drug Release Profile of Ondansetron HCl Marketed Tablet and Optimized Formulation (F-VII)

Discussion

The percentage drug release of marketed sample and optimized formulation (F-VII) was found to be 82.52±0.43 and 99.85±0.07% at 10 minutes.

The drug release of optimized formulation of Ondansetron HCl orally disintegrating tablets was found to be greater than that of marketed product. The percentage drug release was found to be increased by 17.33% at 10 minutes interval in optimized formulation compared to the marketed product.

5.4.4. STABILITY STUDIES

The optimized formulation (F-VII) was selected for the stability study and stored at 25 ± 2°C/60% ± 5% RH and 40 ± 2°C/75% ± 5% RH for a period of three months. The tablets were evaluated for various parameters like physical appearance, average weight, thickness, hardness, friability, disintegration, *in vitro* dispersion, fineness of dispersion, dissolution and assay at every one month interval. The results are presented in table: 30 and 31.

Table: 30 Stability Data of Ondansetron Hydrochloride ODT^S Stored at 25 ± 2°C/60% ± 5% RH (F-VII)

S. No.	Storage Conditions: 25 ± 2°C/60% ± 5% RH				
	Tests	**Initial period**	**1st month**	**2nd month**	**3rd month**
1.	Physical appearance*	Complies	Complies	Complies	Complies
2.	Average weight (mg)	141.50	140.37	140.89	140.11
3.	Thickness (mm)	3.30	3.30	3.30	3.30
4.	Hardness (kg/cm^2)	3.00	3.00	3.00	3.00
5.	Friability (%)	0.15	0.17	0.25	0.22
6.	Disintegration test (sec)	12	12	14	11
7.	*In vitro* dispersion time (sec)	24	25	24	23
8.	Fineness of Dispersion	Passed	Passed	Passed	Passed
9.	*In vitro* drug release at the end of 10 min (%)	99.85	99.82	99.76	99.70
10.	Assay (Limit: 90 to110%)	99.87	99.82	99.75	99.72

***Physical appearance:** Pale orange, Uncoated, Round shaped tablets.

Table: 31 Stability Data of Ondansetron Hydrochloride ODT^S Stored at 40 ± 2°C/75% ± 5% RH (F-VII)

S. No.	Storage Conditions: 40 ± 2°C/75% ± 5% RH				
	Tests	**Initial period**	**1st month**	**2nd month**	**3rd month**
1.	Physical appearance*	Complies	Complies	Complies	Complies
2.	Average weight (mg)	141.50	140.97	142.37	141.28
3.	Thickness (mm)	3.30	3.36	3.30	3.32
4.	Hardness (kg/cm^2)	3.00	3.00	3.00	3.00
5.	Friability (%)	0.15	0.20	0.19	0.23
6.	Disintegration test (sec)	12	12	10	08
7.	*In vitro* dispersion time (sec)	24	24	24	23
8.	Fineness of Dispersion	Passed	Passed	Passed	Passed
9.	*In vitro* drug release at the end of 10 min (%)	99.85	99.76	99.70	99.60
10.	Assay (Limit: 90 to110%)	99.82	99.78	99.75	99.72

***Physical appearance:** Pale orange, Uncoated, Round shaped tablets

Discussion

Stability studies revealed that there were no significant changes found in physical appearance, average weight, thickness, hardness, friability, disintegration test, *in vitro* dispersion test, uniformity of dispersion, dissolution and assay during the period of 3 months even after stored at 25 ± 2°C/60% ± 5% RH and 40 ± 2°C/75% ± 5% RH. The study revealed that the formulation F-VII was stable even stored at 25 ± 2°C/60% ± 5% RH and 40 ± 2°C/75% ± 5% RH for 3 months.

CHAPTER-6

Summary and Conclusion

CHAPTER-6

6. SUMMARY AND CONCLUSION

The present study was undertaken to formulate Ondansetron hydrochloride orally disintegrating tablets by direct compression method using three superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate. The study was aimed to prevent inherent drawbacks associated with conventional tablets of Ondansetron hydrochloride such as risk of choking, bitter taste and difficult in swallowing by formulating Ondansetron hydrochloride ODT^{S}.

A total of seven formulations were prepared to achieve rapid oral disintegration of Ondansetron hydrochloride (three trials by addition of mannitol anhydrous, three trials by sorbitol granular grade and one trial by both mannitol anhydrous and microcrystalline cellulose (MCC-112).

The preformulation study of API such as organoleptic properties, solubility, compatibility study and FT-IR drug- excipients interaction study were carried out.

The prepared blend were also evaluated for precompression parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio.

The prepared tablets were evaluated for post compression parameters such as thickness, hardness, weight variation, friability, disintegration, wetting time and water absorption ratio, *in vitro* dispersion time, fineness of dispersion, assay and *in vitro* drug release.

From the experimental results the following points can be summarized,

- In the preformulation study Ondansetron HCl showed similar color, taste and odor as per the I.P specification. The results of drug excipients compatibility study showed that the excipients selected for the formulation were compatible with the API and suitable for formulation development.

- FT-IR spectral studies of pure drug and drug with excipients showed that there was no interaction between the drug and excipients used in the formulation.
- The results of micromeritic properties indicates that the flow property of formulation F-I was fair and other formulations were good.
- All formulations possessed uniform thickness. The prepared tablets also possessed good mechanical strength with sufficient hardness.
- All formulations of Ondansetron hydrochloride ODT^S passed the weight variation and friability test.
- Disintegration time of Ondansetron hydrochloride ODT^S were found between 12 to 28 seconds. Formulation F-VII showed least disintegration time (12 sec) compared with all other formulations.
- Wetting time and water absorption ratio of Ondansetron hydrochloride ODT^S were found to be in the range between 45 to 102 seconds and 79.25 to 92.17 respectively. Formulation F-VII prepared by using crospovidone as superdisintegrant showed least wetting time (45 sec) and good water absorption ratio among all formulations.
- In the *in vitro* dispersion time evaluation, formulation F-VII showed rapid dispersion time (24 sec) compared with all other formulations.
- All formulations of Ondansetron hydrochloride ODT^S passed the fineness of dispersion test.
- The assay values of Ondansetron hydrochloride tablets were found within the acceptable limits (98.82 to 99.87%).
- In the *in vitro* drug release study, formulation F-VII prepared using crospovidone as superdisintegrant showed maximum drug release (99.85%) at the end of 10 minutes.
- The order of enhancement of dissolution rate with various superdisintegrants was found to be CP>CCS>SSG.

- The obtained data suggested that the formulation containing crospovidone as superdisintegrant showed better disintegration time, *in vitro* dispersion, wetting time and *in vitro* drug release.
- Hence formulation F-VII was considered as the optimized formulation based on rapid disintegration time, wetting time, *in vitro* dispersion and drug release.
- Comparative study of optimized formulation (F-VII) and marketed product was carried out. The *in vitro* drug release of optimized formulation (F-VII) was rapid (99.85%) compared to the marketed product (82.52%) at 10 minutes. From the results, it was concluded that the formulation F-VII showed rapid drug release compared to the marketed product.
- The stability study of optimized formulation (F-VII) indicated that there was no significant changes found in physical appearance, thickness, hardness, average weight, friability, disintegration, *in vitro* dispersion, fineness of dispersion, assay and *in vitro* drug release. The result showed that the optimized formulation (F-VII) was stable even after stored at $25 \pm 2°C/60\% \pm 5\%$ RH and $40 \pm 2°C/75\% \pm 5\%$ RH for a period of 3 months.

CONCLUSION

From the overall results, the study concluded that orally disintegrating tablets of Ondansetron hydrochloride could be successfully formulated by direct compression method using crospovidone as superdisintegrant, which could be a promising formulation to effectively treat nausea and vomiting caused by cytotoxic agent, thereby preventing inherent drawbacks associated with conventional tablets such as risk of choking, bitter taste and difficult in swallowing, also providing faster disintegration, rapid release, bypassing first pass effect, improve patient compliance and therapeutic effectiveness.

From all the above observation it was concluded that the formulation F-VII containing crospovidone as superdisintegrant along with mannitol and microcrystalline cellulose as diluent was found to be better one compared to the other formulations and satisfied the criteria for orally disintegrating tablets.

CHAPTER-7

Future Plan

CHAPTER-7

7. FUTURE PLAN

Formulation (F-VII) may be further investigated for following studies:

- Long term stability study as per ICH guidelines.
- Scale up studies of the optimized formulation F-VII.
- The treatment of nausea and vomiting caused by cytotoxic chemotherapy drugs using the developed tablet formulation.
- Ondansetron hydrochloride orally disintegrating tablet formulations may be evaluated for various Pharmacokinetic parameters.

CHAPTER 8

Bibliography

CHAPTER-8

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